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Clinical trials, practice and design in gastrointestinal cancers

Edited by
Alberto Puccini, Edouard Auclin and Jorg Kleeff

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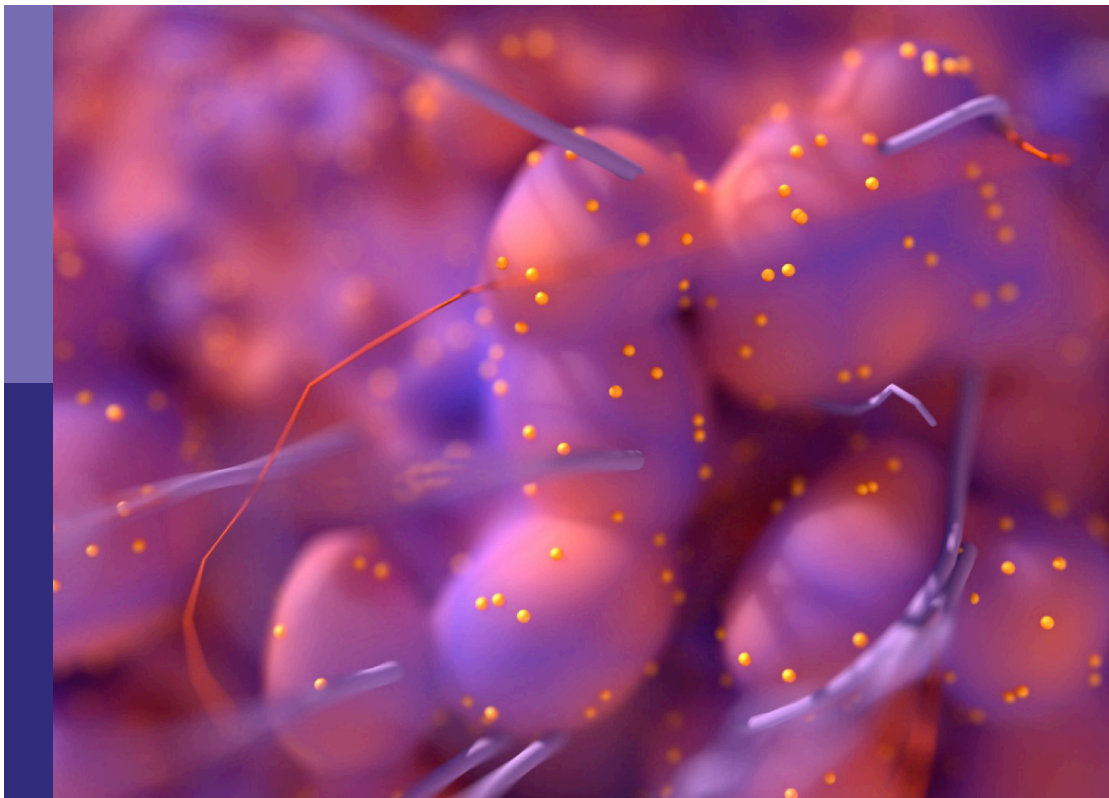

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Clinical trials, practice and design in gastrointestinal cancers

Topic editors

Alberto Puccini — Ospedale Policlinico San Martino IRCCS, Italy
Edouard Auclin — Hôpital Européen Georges-Pompidou, France
Jorg Kleeff — University Hospital in Halle, Germany

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Min Jung Kim,
College of Medicine, Seoul National University, South Korea
Ingrid Garajova,
University Hospital of Parma, Italy

*CORRESPONDENCE
Inne H.M. Borel Rinkes
i.h.m.borelrinkes@umcutrecht.nl
Onno Kranenburg
o.kranenburg@umcutrecht.nl

†These authors have contributed equally to this work

‡These authors share senior authorship

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Consensus molecular subtype 4 (CMS4)-targeted therapy in primary colon cancer: A proof-of-concept study

Niek A. Peters[1†], Alexander Constantinides[1†], Inge Ubink[1†], Joyce van Kuik[2], Haiko J. Bloemendal[3,4], Joyce M. van Dodewaard[3], Menno A. Brink[5], Thijs P. Schwartz[5], Martijn P.J.K. Lolkema[6], Miangela M. Lacle[2], Leon M. Moons[7], Joost Geesing[8], Wilhelmina M.U. van Grevenstein[9], Jeanine M. L. Roodhart[1,10], Miriam Koopman[10], Sjoerd G. Elias[11], Inne H.M. Borel Rinkes[1,9*‡] and Onno Kranenburg[1*‡]

[1]Lab Translational Oncology, Division of Imaging and Cancer, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [2]Department of Pathology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [3]Department of Internal Medicine, Meander Medical Center, Amersfoort, Netherlands, [4]Department of Internal Medicine/Oncology, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands, [5]Department of Gastroenterology, Meander Medical Center, Amersfoort, Netherlands, [6]Department of Medical Oncology, Erasmus Medical Center, Rotterdam, Netherlands, [7]Department of Gastroenterology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [8]Department of Gastroenterology, Diakonessenhuis, Utrecht, Netherlands, [9]Department of Surgical Oncology, Division of Imaging and Cancer, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [10]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [11]Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Background: Mesenchymal Consensus Molecular Subtype 4 (CMS4) colon cancer is associated with poor prognosis and therapy resistance. In this proof-of-concept study, we assessed whether a rationally chosen drug could mitigate the distinguishing molecular features of primary CMS4 colon cancer.

Methods: In the ImPACCT trial, informed consent was obtained for molecular subtyping at initial diagnosis of colon cancer using a validated RT-qPCR CMS4-test on three biopsies per tumor (Phase-1, n=69 patients), and for neoadjuvant CMS4-targeting therapy with imatinib (Phase-2, n=5). Pre- and post-treatment tumor biopsies were analyzed by RNA-sequencing and immunohistochemistry. Imatinib-induced gene expression changes were associated with molecular subtypes and survival in an independent cohort of 3232 primary colon cancer.

Results: The CMS4-test classified 52/172 biopsies as CMS4 (30%). Five patients consented to imatinib treatment prior to surgery, yielding 15 pre- and 15 post-treatment samples for molecular analysis. Imatinib treatment caused significant suppression of mesenchymal genes and upregulation of genes encoding

epithelial junctions. The gene expression changes induced by imatinib were associated with improved survival and a shift from CMS4 to CMS2.

Conclusion: Imatinib may have value as a CMS-switching drug in primary colon cancer and induces a gene expression program that is associated with improved survival.

KEYWORDS

colorectal cancer, consensus molecular subtype 4, imatinib, ImPACCT, platelet-derived growth factor receptor (PDGFR)

Introduction

Large-scale gene expression profiling of colon cancer has identified recurrent patterns of gene expression that form the basis for 'molecular subtyping'. The Consensus Molecular Subtype (CMS) classification system distinguishes four subtypes (CMS1-4) that differ in prognosis and response to systemic therapy (1–4). The gene expression programs that distinguish CMS1-4 also provide opportunities for developing CMS-specific targeted therapies. CMS4 tumors have the highest propensity for developing distant metastases (1), and are characterized by a high content of stromal fibroblasts and, consequently, high expression of mesenchymal genes (5, 6). Candidate molecules for developing CMS4-targeted therapy include the receptor tyrosine kinases (RTKs) Platelet-Derived Growth Factor Receptor alpha and beta (PDGFRA, PDGFRB) and c-KIT (7–9). Indeed, a 4-gene RT-qPCR diagnostic test, which measures PDGFRA, PDGFRB, PDGFC, and KIT, identifies CMS4 CRC with very high sensitivity and specificity (9). Small molecule inhibitors of PDGFR/KIT-family RTKs (e.g. imatinib) are routinely being used for the treatment of gastrointestinal stromal tumors (GIST) and some leukemias, but not CRC (10). In pre-clinical studies, inhibition of PDGFR/KIT signaling reduces tumor cell invasion and metastatic potential in models of mesenchymal-like CRC (7, 8, 11) and other cancer types (12–14), suggesting that imatinib may have value as a CMS4-targeting drug.

The development of CMS4-targeting therapeutic strategies is complicated by intra-tumor CMS heterogeneity. Indeed, many colon tumors consist of CMS4 and non-CMS4 regions (9, 15, 16). Moreover, primary tumors and paired metastases are frequently classified into discordant CMSs (17–19). In addition, radiotherapy and/or chemotherapy may cause a shift in CMS classification (17). To validate the concept of CMS4-targeted therapy, we designed a clinical study in treatment-naïve patients with primary non-metastatic CMS4 colon cancer (ImPACCT; NCT02685046) (20). The aim of ImPACCT was to deliver proof-of-concept that a rationally chosen CMS4-targeting drug has the potential to alter the distinguishing molecular features that are associated with CMS4 colon cancer. Imatinib was selected as a CMS4-targeting drug, based on the very high expression of its targets in CMS4 (this study), its anti-metastatic activity in various pre-clinical models (8, 11, 21), and the potential for rapid future clinical development (22, 23). Comparative analysis of pre- and post-treatment tumor tissue allowed us to assess the effect of imatinib treatment on primary CMS4 colon cancer, and to correlate imatinib-induced gene expression changes with CMS distribution and survival in an independent large colon cancer cohort (1).

Materials and methods

Identification of Imatinib as a candidate CMS4-targeting drug

For the identification of potential therapeutic targets in CMS4 CRC we made use of two independent CRC cohorts [GSE3958215 (24) and TCGA16 (25)] and correlated the CMS4-identifying genes from the random forest classifier with the human kinome ($p < e\text{-}6$). Next, we made use of a publicly available database of kinase inhibitors and their quantitative dissociation constants (Kd) for a large panel of human kinases (26). The inhibitors targeting CMS4 tyrosine kinases were than ranked according to their selectivity scores, defined as the number of kinase hits with a Kd<3 μM divided by the number of kinases tested.

ImPACCT study

The ImPACCT study (NCT02685046) (20) was approved by the medical ethical committee of the University Medical Center Utrecht, the Netherlands (15/527) and the Central Committee on Research Involving Human Subjects (NL50620.041.15). The

study was divided into two phases: (i) the biopsy classification phase and (ii) the imatinib treatment phase.

In the first phase, subjects scheduled for a diagnostic colonoscopy on account of either clinical suspicion of CRC or in accordance with the national colorectal cancer population screening program were approached for permission to obtain five additional endoscopic biopsies. Out of these 5 biopsies, 3 were used for RNA isolation and RT-qPCR CMS4 classification. From the day of biopsy acquisition, it took 3-5 days to complete the procedure and provide a multi-region-based molecular classification.

In the second phase, patients diagnosed with CMS4 colon or rectal cancer were approached again for informed consent to receive neo-adjuvant imatinib treatment.

Patients and samples

Three hospitals (the University Medical Center Utrecht, the Meander Hospital Amersfoort, and the Diakonessenhuis Utrecht) were opened as inclusion centers. Biopsy samples were collected in individual sterile cryotubes and snap-frozen in liquid nitrogen as soon as possible, mostly at the end of the endoscopy procedure. Samples were transported on dry ice and stored at -80°C until further downstream processing.

Patients diagnosed with CMS4 CRC were approached again for informed consent and screening for eligibility for the second phase of ImPACCT, consisting of imatinib treatment. In- and exclusion criteria are provided in Supplementary Table S1. In brief, patients were required to (i) be scheduled for surgery for removal of the primary tumor, (ii) not receive any neoadjuvant therapy, (iii) be in good condition (ECOG Performance Status 0 or 1), and (iv) not have metastatic disease. After a consideration period, written informed consent was obtained for treatment with imatinib. Imatinib was administered orally at a daily dosage of 400 mg for 14 days prior to planned tumour resection.

The study was powered for 27 patients to be treated with imatinib (20). The study was terminated after inclusion of 5 patients for preoperative imatinib therapy due to low accrual rate. All patients included in this analysis gave written informed consent. Clinical data were collected from electronic patient records.

Random forest CMS classification

The random forest CMS classification based on next generation RNA sequencing data was performed as previously described and according to Guinney et al. (1, 9) and can be considered the gold standard. In short, the sequencing libraries were normalized using size-factor normalization using the DESeq2 package (version 3.14) (27) on Bioconductor for R. As the ImPACCT cohort should only consists of CMS4 tumors and the random forest classifier requires a balanced dataset with all subtypes present, we made use of a 'piggyback' dataset of 199 primary CRCs and pooled these with the ImPACCT dataset to perform the CMS classification. To this end, we applied the 273-gene random forest CMS classifier (available at Github, https://github.com/Sage-Bionetworks/crcsc; applied with predict.randomForest, R package randomForest version 4.6-10), obtaining for each sample a predicted probability of belonging to one of the CMS subtypes.

Differential gene expression analysis

For the transcriptomic and principal component analyses, we made use of the R2: Genomics Analysis and Visualization Platform (http://r2.amc.nl). Gene set enrichment analyses were performed using the MSigDB hallmark genesets collection (n=50) (28) and the immune compendium signature collection (29). Differentially expressed signatures were identified using ANOVA and significance levels were corrected using the Bonferoni-method (p-value cutoff ≤0.001).

Differentially expressed genes between pre- and post-imatinib samples were identified using ANOVA with multiple comparison correction using FDR $p \leq 0.001$. For the comparison between pre- and post-imatinib biopsies the following signatures were used: 4-gene CMS4 test signature, Desmosome, circulating cell cluster (30), WNT (31), KEGG adherens junctions (32), KEGG cell cycle (32), MSigDB hallmark MYC targets v1 and MTORC1 signaling (28), mTOR TOP targets (33), and CMS4 upregulated genes (1) (Supplementary Table S2).

Statistical analysis

Statistical analysis was performed using GraphPad Prism (software version 9) or R version 4.1.1 for Mac (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). Differential gene expression and principal component analyses were performed in the R2 Genomics platform (http://r2.amc.nl). To study imatinib induced transcriptional changes in the context of CMS subtypes, we used an independent publicly available large CRC cohort of n = 3232 patients [CMS-3232 (1)]. Differentially upregulated genes after imatinib therapy were used to cluster the CMS-3232 cohort into a low- and high-expression subgroup using the k-means cluster algorithm. For comparisons between pre- and post-imatinib biopsies a linear mixed model was used to account for clustering effects within patients using a random intercept per patient. Associations between continuous variables were assessed using marginal Pearson correlation coefficients for clustered data (34). Data were compared using two-sided Pearson χ^2, Fisher's exact, Student's t, or Mann-Whitney-U-test as appropriate. Results with p-values smaller than 0.05 were considered statistically significant (*). All statistical tests

performed in this study were two-sided. P-values smaller than 0.01, 0.001, and 0.0001 are indicated by (**), (***), and (****), respectively.

Results

Identification of imatinib as a candidate CMS4-targeting drug

To search for potential therapeutic targets in CMS4 CRC we focused on the human kinome. Expression of 55 kinases (22 tyrosine kinases (TK)) was positively correlated with expression of CMS4 signature genes in two independent colon cancer cohorts (p<e-6; Supplementary Table S3). A large number of TK inhibitors (TKIs) are approved and available for the treatment of cancer and other diseases. By applying a dataset of quantitative dissociation constants (Kd) of drug-target interactions for 72 distinct kinase inhibitors (26) a list of candidate CMS4-targeting TKIs was identified containing six FDA-approved anti-cancer drugs (Supplementary Table S4). Ranked from high-to-low selectivity for inhibiting CMS4 TKs, these are imatinib, nilotinib, sorafenib, pazopanib, vandetanib, and dasatinib (Supplementary Table S4; Supplementary Figure S1). None of these TKIs are currently indicated for the treatment of colon or rectal cancer. Of the 6 candidate CMS4-targeting drugs, imatinib was the most selective, targeting PDGFRA, PDGFRB, KIT and the collagen receptor DDR2 in the lower nanomolar range (Supplementary Table S5). Based on this analysis, the available toxicity data, and the reported anti-tumorigenic and anti-metastatic activity in pre-clinical colon cancer models (8, 11, 21–23), imatinib was chosen as CMS4-targeting drug in ImPACCT.

Selection of patients with CMS4 colon cancer at initial diagnosis

Between August 2016 and August 2019, approximately 1500 individuals who were scheduled for colonoscopy were approached for informed consent for the acquisition of additional biopsies for molecular diagnosis using a validated 4-gene RT-qPCR CMS4 test (9) (Figure 1). In total, 350 endoscopic biopsies were collected from 70 tumors from 69 patients (Figure 1 and Supplementary Table S6). Of these, 63 tumors from 62 patients were histologically confirmed colorectal cancer (58 colon; 5 rectum) and used for CMS4 testing (Table 1).

To account for intra-tumor CMS heterogeneity RNA was isolated from 195 biopsies from 63 tumors. This yielded 172 RNA samples of sufficient quantity and quality for subsequent CMS4 testing. Of these 172 biopsies, 52 (30%) were classified as CMS4 (Figure 2). Different regions from the majority of individual tumors displayed considerable variation in CMS4 probability (Figure 2). After calculating the weighed mean CMS4 probability of 2-3 biopsies per tumor, 24 of the 63 evaluable tumors (38%) were classified as CMS4 (Figure 2; Table 1). CMS4 tumors were diagnosed significantly more frequently in younger patients (< 0.001) and in left-sided colon cancers (p<0.001) (Table 1). Moreover, micro-satellite instability (MSI) was detected significantly less frequently in CMS4 versus non-CMS4 tumors (2/20 vs. 11/29; p=0.047). The fraction of CMS4 tumors increased with higher TNM stage (Supplementary Figure S2). Although this trend did not reach statistical significance, it is in line with a previous report (35). All 9 biopsies obtained from three adenomas were classified as non-CMS4 (Figure 2).

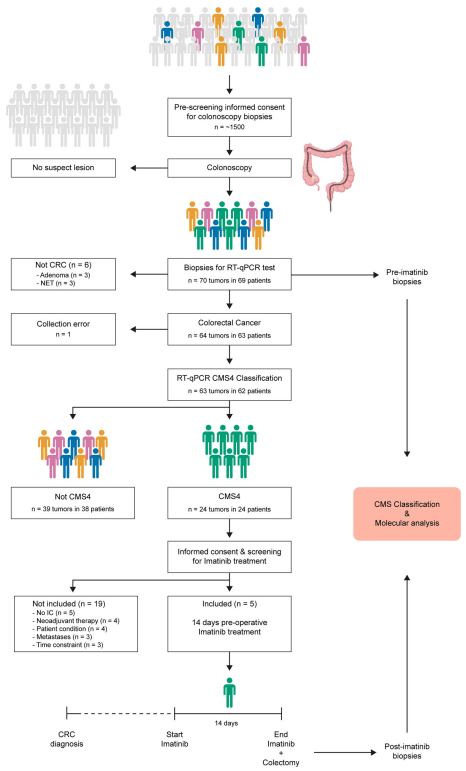

FIGURE 1
ImPACCT study flowchart. Individuals scheduled for a colonoscopy procedure were approached to obtain informed consent for acquisition of 5 additional biopsies for CMS4 testing in case suspect lesions were found, and for approval to approach them again in case the tumor was diagnosed as CMS4. Patients with CMS4 CRC were approached to obtain informed consent for the second part of the study (imatinib treatment), and were screened for eligibility. Five patients received imatinib treatment for 14 days prior to surgery. Pre-treatment diagnostic biopsies and post-treatment biopsies from the resected primary tumors were used for CMS classification and additional molecular analyses.CMS, consensus molecular subtype; RT-qPCR, real-time quantitative polymerase chain reaction; IC, informed consent; CRC, colorectal cancer.

TABLE 1 Characteristics of colorectal cancer patients biopsied for CMS4 identification.

Characteristic	Not CMS4, N = 39[1]	CMS4, N = 24[1]	p–value[2]
Age at diagnosis	74 (52–86)	62 (48–83)	<0.001
Sex			0.35
Male	22 (58)	11 (46)	
Female	16 (42)	13 (54)	
Diagnosis			>0.99
Colorectal Cancer	39 (100)	24 (100)	
Adenoma	0 (0)	0 (0)	
Neuroendocrine tumor	0 (0)	0 (0)	
Histology			0.29
Adenocarcinoma	25 (68)	21 (91)	
Mucinous adenocarcinoma	8 (22)	2 (8.7)	
Signet–ring cell	2 (5.4)	0 (0)	
Other	1 (2.7)	0 (0)	
Not reported	1 (2.7)	0 (0)	
Sidedness			0.003
Right colon	26 (67)	6 (25)	
Left colon	11 (28)	15 (62)	
Rectum	2 (5.1)	3 (12)	
AJCC TNM Stage			0.62
1	7 (19)	3 (12)	
2	12 (32)	5 (21)	
3	15 (41)	13 (54)	
4	3 (8.1)	3 (12)	
Differentiation			>0.99
Well	0 (0)	0 (0)	
Well–moderate	28 (88)	21 (91)	
Moderate	2 (6.2)	1 (4.3)	
Poor	0 (0)	0 (0)	
Undifferentiated	2 (6.2)	1 (4.3)	
MSI			0.047
MSS	18 (62)	18 (90)	
MSI	11 (38)	2 (10)	
Heterogeneity in CMS4 status of biopsies	6 (15)	14 (58)	<0.001
(Serious) Adverse Event after colonoscopy	0 (0)	1 (4.2)	0.39
Underwent surgery	33 (89)	23 (96)	0.64
Procedure			<0.001
Abdominoperineal Resection	0 (0)	1 (4.3)	
Extended Hemicolectomy	4 (12)	0 (0)	
Hemicolectomy Left	2 (6.2)	3 (13)	
Hemicolectomy Right	16 (50)	5 (22)	
Low Anterior Resection	0 (0)	9 (39)	
Sigmoid Resection	8 (25)	5 (22)	
Transverse Colectomy	2 (6.2)	0 (0)	
Laparoscopic			0.34
Open	3 (9.4)	5 (22)	
Laparoscopic	23 (72)	14 (61)	
Laparoscopic converted to open	6 (19)	3 (13)	
Robot	0 (0)	1 (4.3)	

(Continued)

TABLE 1 Continued

Characteristic	Not CMS4, N = 39[1]	CMS4, N = 24[1]	p–value[2]
Primary anastomosis	32 (100)	17 (74)	0.003
Length of stay (days)	5.5 (2.0–38.0)	5.0 (3.0–42.0)	0.92
Complications Clavien Dindo >II	14 (42)	8 (35)	0.56
90–day mortality	0 (0)	1 (4.3)	0.43
Pre–operative Imatinib Therapy	0 (0)	5 (21)	n.a.

[1]Median (Minimum–Maximum), n (%).
[2]Wilcoxon rank sum test, Pearson's Chi–squared test, Fisher's exact test, where appropriate. n.a., not applicable.

Neoadjuvant imatinib therapy

All patients with CMS4 tumors were approached to obtain informed consent for inclusion in the second phase of the study: two weeks preoperative imatinib treatment. Of the 24 patients whose primary tumors were classified as CMS4 at first diagnosis, 14 were ineligible for the second part of the study, because i) they received neoadjuvant chemotherapy (n=4), ii) the patients were in poor condition (n=4), iii) distant metastases were detected (n=3), or iv) the preoperative window was shorter than 2 weeks (n=3). Of the remaining 10 patients with primary CMS4 CRC, 5 patients (all colon cancer) consented to participate in the second phase of the study and received 14 days of imatinib treatment prior to surgical removal of the primary tumor (Figure 1, Table 2). No serious adverse events were observed during imatinib therapy. Minor adverse events were observed in 3 patients and included fatigue, edema, eye irritation, nausea, and dizziness.

Peri- and postoperative adverse events were documented in 4 patients and included gastroparesis and stomach ache. One patient underwent an extensive multivisceral resection involving the rectosigmoid, a portion of the vagina, the upper bladder wall, and the adnex. This patient experienced intra-operative haemorrhage which was followed by admission to the intensive care unit (ICU) and an extended postoperative hospital stay. Given the extent of the surgical procedure, the relationship of these adverse events with imatinib treatment is unlikely. Median follow-up time in the CMS4 and non-CMS4 groups were 34.2 months and 37.1 months respectively. 2-year overall-survival (OS) in the CMS4 and non-CMS4 groups were 86.7% (95%-CI, 73.8% - 100%) and 71.7% (95%-CI, 58.2% - 88.3%) respectively. Kaplan Meier survival estimates were not significantly different between the 2 groups (p=0.29; Supplementary Figure S3). Within the CMS4 group, overall survival between imatinib-treated and untreated patients was not significantly different (Supplementary Figure S3).

Imatinib treatment shifts CMS4 tumors to a more epithelial phenotype

Pre-treatment biopsies (obtained during diagnostic colonoscopy) and post-treatment biopsies (obtained from the surgical resection specimen) were processed for RNA isolation and RNA sequencing. Molecular subtyping of the samples by

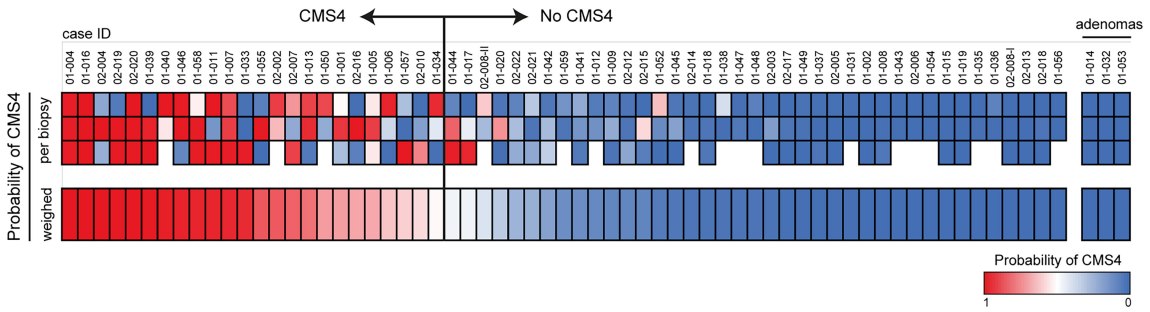

FIGURE 2
. CMS4 assessment on diagnostic biopsies and patient selection. Diagnostic biopsies (3 per tumor) were processed for RNA isolation and subsequent CMS4 testing, using a previously designed and validated RT-qPCR test (9). The heatmap shows CMS4 probabilities per-biopsy (top) and the weighed mean probabilities per tumor, to account for intra-tumor CMS4 heterogeneity. If the weighed mean probability was higher than 50%, tumors were classified as CMS4 (n=24) and the patients were approached for the second part of the study. The cohort contained 3 histologically confirmed adenomas (right sub-panel).

TABLE 2 Characteristics of CMS4 colon cancer patients who received neoadjuvant imatinib therapy.

Characteristic	N = 5[1]
Age at diagnosis, No. (%)	56.0 (48.0–62.0)
Sex	
Male	3 (60)
Female	2 (40)
Height (cm), median (min–max)	178.0 (164.0–183.0)
Weight (kg), median (min–max)	95 (76–126)
ECOG status, No. (%)	
WHO 0	3 (60)
WHO 1	2 (40)
Location, No. (%)	
Caecum	1 (20)
Sigmoid	3 (60)
Transverse colon	1 (20)
Tumor stage, No. (%)	
T3	4 (80)
T4	1 (20)
Nodal stage, No. (%)	
N0	1 (20)
N1	2 (40)
N2	2 (40)
Metastatic stage, No. (%)	
M0	5 (100)
AJCC TNM Stage, No. (%)	
2	1 (20)
3	4 (80)
Differentiation, No. (%)	
Moderate	2 (40)
Well	3 (60)
Procedure, No. (%)	
Hemicolectomy Left	1 (20)
Hemicolectomy Right	1 (20)
Low Anterior Resection	2 (40)
Sigmoid Resection	1 (20)
Length of stay (days), median (min–max)	8.0 (4.0–18.0)
Complications Clavien Dindo >II, No. (%)	3 (60)
Adverse Events, No. (%)	3 (60)
Serious Adverse Events, No. (%)	1 (20)
90–day mortality, No. (%)	0 (0)

[1]Median (Minimum–Maximum), n (%)

applying the random forest CMS classifier revealed that pre-treatment samples were classified either as CMS4, or as indeterminable (if the probability of none of the subtypes was more than 0.5) (Figure 3A). The CMS4 probabilities of the pre-treatment samples showed a strong and significant correlation with the CMS4 scores that were generated by the CMS4 4-gene RT-qPCR test (ρ_m=0.80, p<0.0001; Figure 3B). Of the 15 biopsies analysed prior to treatment none were classified as CMS1-3. However, after imatinib treatment 6 of the 15 biopsies (40%) were classified as CMS1 (n=2) or CMS2 (n=4), while the incidence of CMS4 biopsies was reduced from 55% to 33% (Figure 3A). Overall, imatinib treatment caused a reduction of the average CMS4 probability, although this was not statistically significant (Figure 3C). However, we did observe a significantly reduced expression of the 4 CMS4-identfying genes in the RT qPCR test that was used to include the patients (Figure 3C). Moreover, expression of specific mesenchymal genes such as ZEB1, PDGFRA, PDGFRB, and CD36 was strongly and significantly reduced after imatinib treatment (Figure 3D). Epithelial cell-cell contacts are mediated by adherens junctions, desmosomes and tight junctions. Expression of *CDH1* and *CTNNA1*, encoding the adherens junction components E-cadherin and alpha-catenin, and an adherens junction signature, was significantly increased following imatinib treatment (Figure 3E). Likewise, expression of the desmosome gene *JUP*, encoding Plakoglobin, and a desmosome signature was also significantly higher following imatinib treatment (Figure 3E). Moreover, an independent signature distinguishing circulating tumor cell clusters from single cells, was also significantly higher in post-treatment samples (Figure 3E). By contrast, expression of genes encoding tight junction proteins did not change following imatinib treatment. Expression of CDH1 was inversely correlated with CMS4 probability (Figure 3F). Expression of the key EMT-driving transcription factor ZEB1 was strongly reduced following imatinib treatment in 3/5 patients (Figure 3G), similar to what we have previously observed in pre-clinical CRC models (8). Biopsies with the highest ZEB1 expression were mostly derived from pre-treatment tumors (8/11; 73%), while biopsies with the lowest ZEB1 expression were all derived from post-treatment tumors (9/9; 100%) (Figure 3G).

Mesenchymal tumor phenotypes are generally accompanied by reduced proliferation. Indeed, high expression of proliferation signatures and Wnt target genes are associated with good prognosis and reduced metastatic capacity in CRC (36–38). To further elucidate this observation in the context of CMS subtypes in CRC, we made use of a publicly available dataset of 3232 primary colon cancers (CMS-3232). In line with this notion, we found that expression of the generic proliferation marker MKI67, WNT- and MYC-target genes, and the KEGG pathway 'cell-cycle' are expressed at significantly lower levels in CMS4 than in any of the other subtypes in primary colon cancer (Figure 4A). Moreover, expression of CMS4-identifying genes from the random forest classifier were inversely correlated to expression of genes in the KEGG pathway 'cell-cycle' (R = -0.34, p<2e-16; Figure 4B). In ImPACCT, imatinib treatment of CMS4 tumors caused a significant increase in the expression of MKI67, WNT- and MYC-target genes, and KEGG pathway cell cycle genes (Figure 4C).

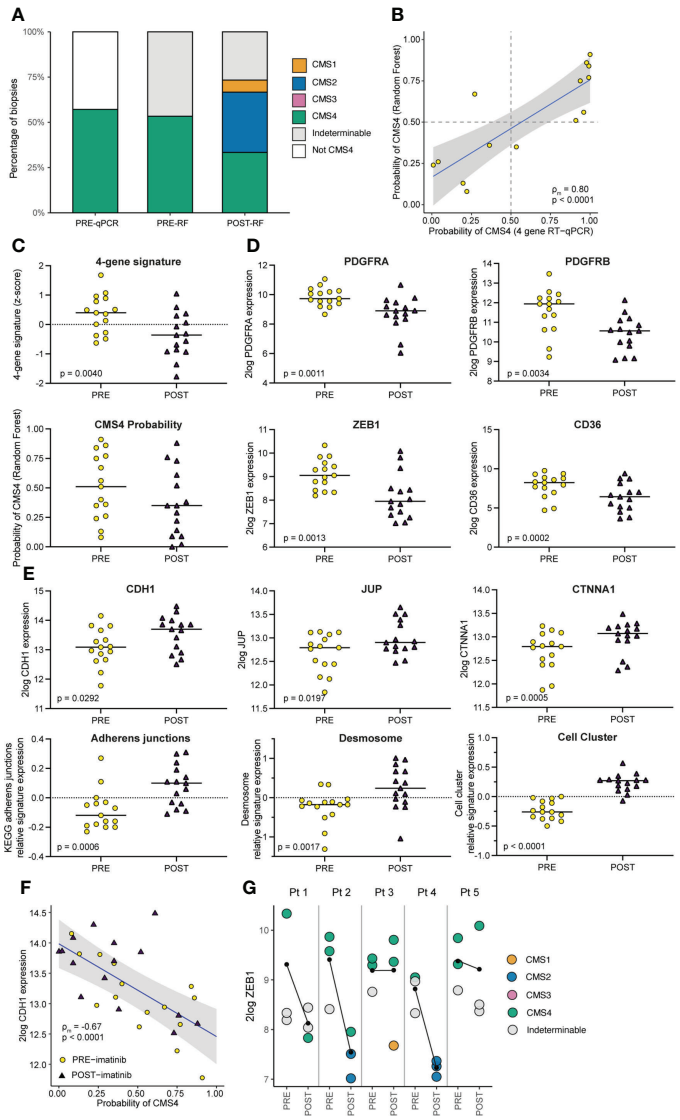

FIGURE 3
Imatinib treatment of primary CMS4 CRC results in a mesenchymal-to-epithelial phenotype shift. **(A)** Bar graph summarizing CMS classification of tumor tissue samples PRE and POST imatinib treatment, measured by the RT-qPCR test and the CMS random forest (RF) classifier applied to RNA sequencing data. **(B)** XY-plot showing the correlation between CMS4 probabilities of pre-treatment diagnostic biopsies as measured by the RT-qPCR test and the RF classifier. ρ_m denotes the marginal Pearson correlation coefficient for clustered data (34) with two-sided p-value. **(C)** Dot-plots showing expression (mean z-scores) of a signature comprised of the 4 genes in the CMS4 test (*PDGFRA, PDGFRB, PDGFC, KIT*) and the CMS4 probabilities generated by the RF classifier, in tissue samples PRE and POST imatinib treatment. P values were generated using ANOVA and a linear mixed model. **(D)** Dot plots showing 2log expression levels of *PDGFRA*, *PDGFRB*, *ZEB1*, and *CD36* in tissue samples PRE and POST imatinib treatment. P values were generated using a two-sided Student's *t*-test. **(E)** Dot plots Graphs showing 2log expression values of epithelial junction genes (*CDH1*, *JUP*, and *CTNNA)* and expression of signatures for Adherens Junctions, Desmosomes, and genes upregulated in epithelial cell clusters versus single cells in tissue samples PRE and POST imatinib treatment. P values were generated using ANOVA and a linear mixed on pre- vs post-treatment biopsies. **(F)** XY-plot showing the (negative) correlation between *CDH1* expression and CMS4 probabilities (RF) in tissue samples PRE and POST imatinib treatment. ρ_m denotes the marginal Pearson correlation coefficient for clustered data with two-sided p-value. **(G)** Dot plot showing *ZEB1* expression in tissue samples PRE and POST imatinib treatment in individual patients with color-coded CMS classification. The black lines indicate the change in mean *ZEB1* expression following imatinib treatment.

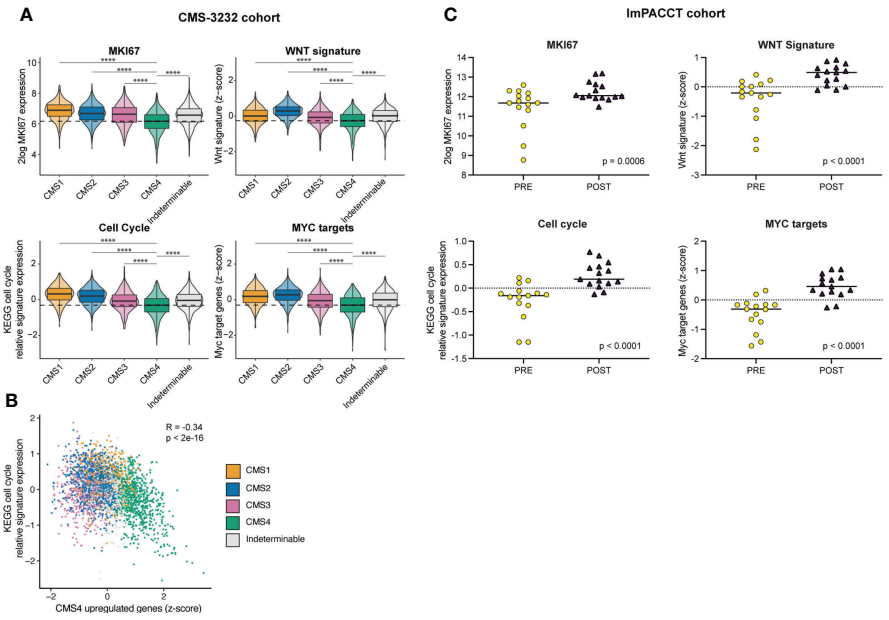

FIGURE 4
Imatinib treatment of primary CMS4 CRC causes increased expression of proliferation-associated genes. **(A)** Tukey box and violin plots showing expression of the proliferation marker *MKI67* and signatures reflecting cell cycle activity (KEGG), WNT target genes (31), and MYC target genes (39) in CMS1–4 in the CMS–3232 cohort. Statistically significant differences were identified using one–way analysis of variance (ANOVA) with subsequent *post–hoc* pairwise comparisons using *t*–tests with pooled SD using Bonferroni multiple comparison p–value adjustment. **(B)** XY–plot demonstrating the (negative) correlation between CMS4–identfying genes in the RF classifier and the KEGG pathway signature genes reflecting cell cycle activity. R denotes the Pearson correlation coefficient with two–sided p–value in the CMS–3232 cohort. CMS1–4 are color–coded. **(C)** As in **(A)** but in the ImPACCT cohort. Statistically significant differences were identified using two–sided ANOVA and a linear mixed model.

Imatinib induces a gene expression program that is associated with improved prognosis

To explore the transcriptomic effects of imatinib treatment in an unbiased fashion, the RNAseq data were subjected to a dimensionality reduction analysis (principal component analysis; PCA). Interestingly, the samples segregated according to treatment status (pre-versus post-treatment) indicating that imatinib therapy had a major effect on global gene expression patterns (Figure 5A). Furthermore, imatinib treatment resulted in significantly increased expression of 10 signatures reflecting specific Cancer Hallmarks (Molecular Signature Database [MSigDB) (39)], including 'mTORC1 signaling' and 'E2F targets' (Figure 5B, Supplementary Figure S4). Of note, these pathways have previously been linked to a mesenchymal-to-epithelial (i.e. invasive-to-proliferative) phenotype shift (40).

Next, we analysed whether imatinib treatment altered the immune landscape of CRC. To this end, we made use of the immune compendium signature collection (29) and found that imatinib treatment did not significantly alter expression of immune-related gene signatures (Figure 5C).

Differential gene expression analysis between pre- and post-treatment biopsies identified 228 significantly upregulated genes following imatinib treatment, and 452 downregulated genes (FDR<0.001; Supplementary Table S7). To assess the potential prognostic value of this shift in 'molecular phenotype' we made use of the CMS-3232 primary CRC cohort with annotated CMS status and survival data (1). The 228 genes upregulated after imatinib treatment were used to cluster the Stage II and III tumors in this cohort into low and high expression subgroups using the k-means algorithm (Figure 5D). The corresponding heatmap (Figure 5E) shows that the genes induced by imatinib are strongly co-regulated in primary CRC. Analysis of the CMS distribution in subgroups expressing high versus low levels of imatinib-induced genes revealed a significantly lower proportion of CMS4 tumors in the high expression subgroup (12% vs. 39%; p < 2.2e-16; Figure 5F). Moreover, relapse-free and overall survival were significantly better in the subgroup expressing high levels of imatinib-induced genes (Figure 5G). Overall, the data suggest that neo-adjuvant imatinib treatment causes a phenotypic (mesenchymal-to-epithelial) shift that is associated with better survival.

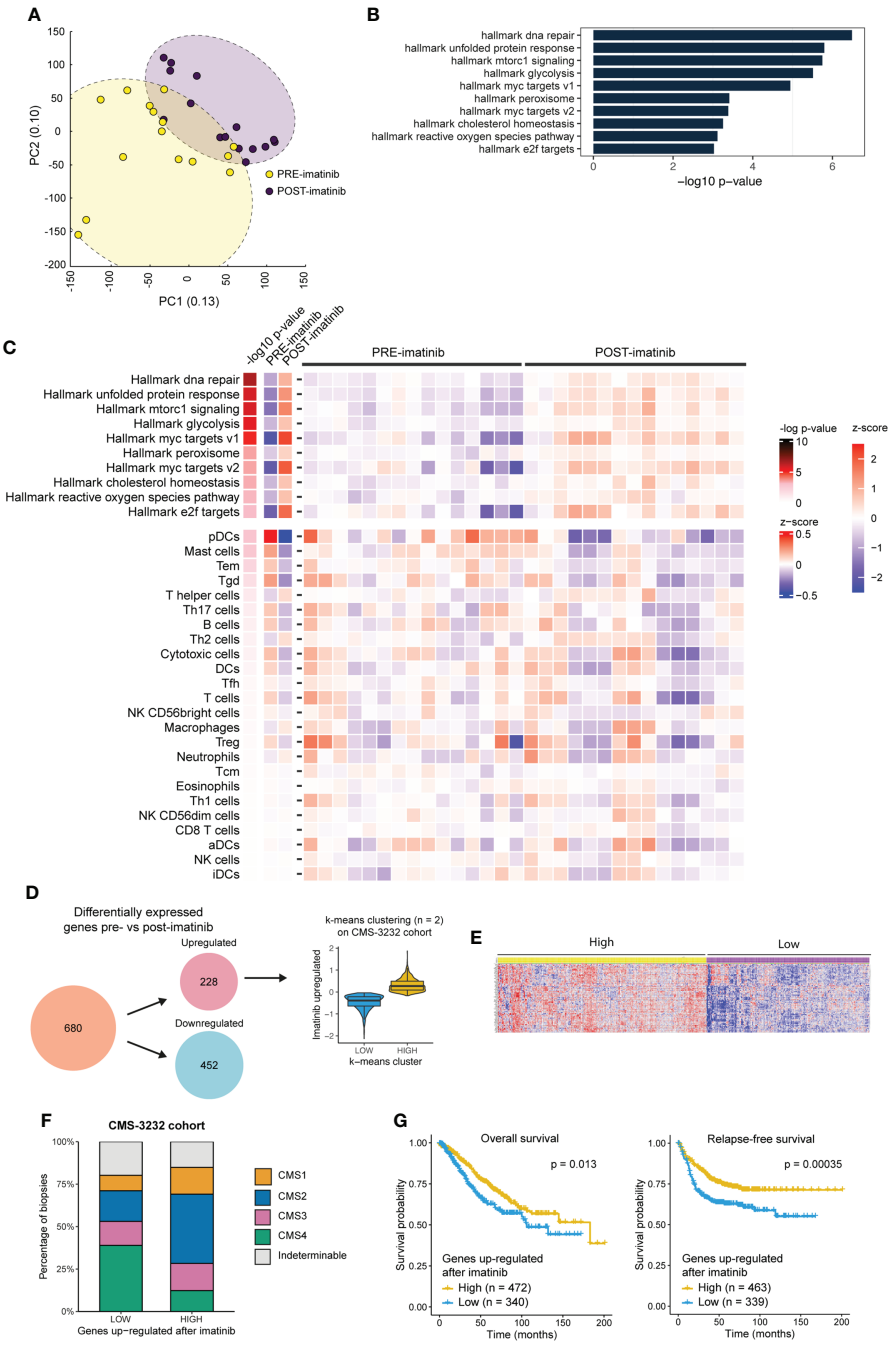

FIGURE 5
Imatinib treatment of primary CMS4 CRC induces a phenotype that is associated with better prognosis. **(A)** Principle component analysis based on expression of all genes. PRE and POST imatinib samples are color−coded. **(B)** Bar plot showing the significant up− and down−regulated cancer hallmark signatures (40) (n = 10/50) between pre− and post−imatinib biopsies ranked according to significance (min−log10 p−values). **(C)** Heatmap showing expression of the 10 significantly upregulated hallmark signatures and a compendium of immune signatures (29) in PRE and POST imatinib treatment samples. **(D)** Differential gene expression analysis (ANOVA FDR p ≤ 0.001) identified 680 differentially expressed genes of which 228 were up− and 452 were down−regulated after imatinib therapy. The 228 imatinib−induced genes were then used to cluster the CMS3232 cohort (1) into LOW and HIGH expression subgroups using the k−means algorithm. **(E)** Heatmap showing expression of imatinib−induced genes in the LOW and HIGH expression subgroups. **(F)** Stacked barplot showing the CMS distribution in subgroups of tumors expressing LOW and HIGH levels of imatinib−induced genes. **(G)** Kaplan Meier curves showing overall (left) and relapse−free (right) survival in subgroups of stage II−III tumors in the CMS3232 cohort (1) expressing LOW and HIGH levels of imatinib−induced genes. A two−sided log−rank test was applied to assess the significance of the survival differences between the two groups.

Imatinib alters mTORC1 signaling

One of the cancer hallmark pathways that was most significantly upregulated in imatinib-treated tumors was 'mTORC1 signalling' (Figures 5B, C). The mTORC1 protein complex plays an essential role in the translation of mRNAs containing a terminal oligo-pyrimidine (TOP) motif, which mainly encode translational initiation and elongation factors and ribosomal proteins necessary for cell growth and proliferation (33). Imatinib treatment significantly increased the expression of virtually all known TOP mRNA mTORC1 targets, as well as expression of three of the five mTORC1 complex subunits (MLST8, DEPTOR, RPTOR) (Figures 6A–F). Expression of the other two mTORC1 subunits was unaltered (MTOR, AKT1S1) (Figures 6G, H). Some of the best characterized substrates for mTORC1 are the ribosomal protein S6 kinases (S6K1 and S6K2) which phosphorylate

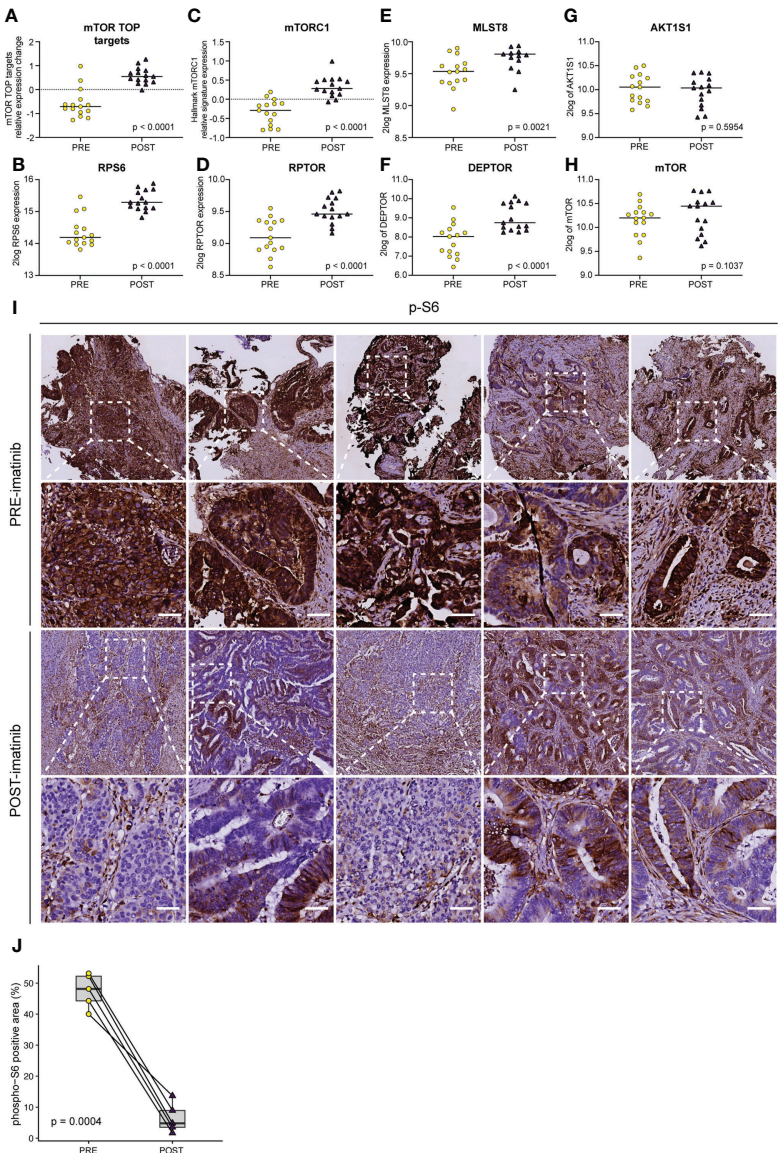

FIGURE 6
Imatinib inhibits ribosomal protein S6 phosphorylation and causes transcriptional activation of the mTORC1 pathway. Expression levels of **(A)** mTORC1 TOP target mRNAs (33), **(B)** ribosomal protein S6 (*RPS6*), **(C)** the Hallmark mTORC1 signature, and the individual mTORC1 components **(D)** *RPTOR*, **(E)** *MLST8*, **(F)** *DEPTOR*, **(G)** *AKT1S1*, and **(H)** *MTOR*. Statistically significant expression differences were identified using ANOVA and a linear mixed model. **(I)** Immunohistochemistry (IHC) for the detection of phosphorylated ribosomal protein S6 (pS6) on PRE–treatment (upper row) and POST–treatment (lower row) biopsies. Representative images of the stained sections are shown. Scale bar, 50 µm **(J)** QuPath software (41) was used to quantify the pS6 IHC signal in the epithelial compartment in pre– and post–imatinib biopsies. Values were then plotted in Tukey boxplots and the significance of the observed staining difference was assessed using a two–sided paired Student's *t*–test.

ribosomal protein 6 (RPS6) and multiple other substrates to control protein translation, cell size and cell survival (42). Importantly, mTORC1 activation of S6K is essential for maintaining proliferation of APC-deficient intestinal adenomas in mice (43). The observed upregulation of mTORC1-encoding genes and the Hallmark mTORC1 pathway suggests that this pathway may have been activated following imatinib treatment. Therefore, we used antibodies recognizing phosphorylated RPS6 (pS6) as a tool for assessing the activity of the mTORC1-S6K pathway in pre- and post-treatment tumor samples *in situ*. Surprisingly, we found that imatinib caused a profound inhibition of S6 phosphorylation in the tumor cells of all post-treatment samples examined (Figures 6I–J).

Discussion

In this study we have provided proof-of-concept that the aggressive phenotype of CMS4 CRC can be mitigated by rationally chosen targeted therapy. The mesenchymal-to-epithelial phenotype shift following imatinib therapy coincided with increased expression of WNT- and MYC-target genes and signatures reflecting proliferation. Accelerated proliferation may – at first sight – not be considered a desired effect of any anti-cancer therapy. However, high expression of proliferation signatures and WNT target genes are associated with good prognosis and reduced metastatic capacity in CRC (36–38). Proliferation and invasion are often inversely regulated in tumor biology, supporting the notion that proliferating tumor cells have to switch their transcriptional state (through EMT) in order to acquire invasive and metastatic properties (40, 44, 45). Proliferating tumor cells require high expression of mTORC1 and its target genes to meet their anabolic demand (46). The high expression of mTORC1 in imatinib-treated tumors may therefore simply reflect the MET phenotype switch. Interestingly, activation of the mTORC1 pathway also plays an important role in acquired resistance to imatinib (47–49). It is therefore possible that the profound inhibition of mTORC1 signaling (*i.e.* reduced S6 phosphorylation) in imatinib-treated tumors has caused activation of a transcriptional feedback program in an attempt to restore pathway activity. Further preclinical work should reveal whether prolonged treatment of CMS4 CRC with imatinib monotherapy indeed leads to re-activation of mTORC1 signaling. Combination treatments consisting of imatinib and mTOR inhibitors are currently being evaluated in clinical trials, although not in colon cancer patients [NCT01275222 and (50)].

Clinical application of the CMS system not only requires the development of effective subtype-targeted therapies, but also the generation of diagnostic tools that allow rapid subtype assessment in routine clinical practice. Several tissue-based diagnostic tools have been developed for clinical CMS stratification (2, 9, 51, 52). However, all methods suffer from the existence of intra-and inter-tumor CMS heterogeneity and, thus, from sampling bias. In the present study we have dealt with this problem by taking a multi-biopsy approach, coupled to a weighing strategy of RT-qPCR test results (9), and have demonstrated the feasibility of identifying primary CMS4 CRC at initial diagnosis on endoscopic biopsies. We have focused on primary colon cancer, because the CMS classification was based on this disease entity (1). However, in patients with metastatic disease, inter- and intra-tumor heterogeneity will pose a more profound problem, simply because tumor load is higher and more diverse, and sampling options are limited. One potential solution would be the design and development of CMS-specific molecular imaging strategies (53).

The ImPACCT study was discontinued due to slow accrual. The major logistical challenge was the requirement to obtain informed consent from every individual prior to colonoscopy. However, only 2-5% of people undergoing a colonoscopy are diagnosed with cancer, and only 25% of these tumors are CMS4 colon cancer. In ImPACCT more than 1.500 people undergoing a colonoscopy had to be approached to ultimately include 5 patients for treatment (0.3%). The inclusion of tissue- or imaging-based molecular subtyping as part of the routine diagnostic workup for primary colon cancer will therefore greatly facilitate future studies developing CMS-targeted therapy.

In conclusion, this study demonstrates the feasibility of mitigating the aggressive biology of CMS4 primary colon cancer with targeted therapy in pre-selected cancer patients. The gene expression changes caused by imatinib treatment were indicative of a mesenchymal-to-epithelial phenotype shift and were associated with better prognosis. A logical next step would be to evaluate whether 'CMS4-switch-therapy' can sensitize CMS4 colon cancer to standard chemotherapy regimens.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found at the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) under the Accession Number GSE3958215.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Review Board in the University Medical Center Utrecht. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: IU, ML, MK, SE, IBR, OK. Data curation: NP, AC, IU, JK, HB, JD, MB, TS, LM, SE, IB, OK. Investigation and experiments: NP, AC, IU, JK. Methodology: SE. Formal analysis: NP, AC, IU, SE, IR, OK. Supervision: HB, JD, JG, IB, OK. Writing – original draft: NP, AC, IU, SE, IB, OK. Writing –

review and editing: NP, AC, IU, JK, HB, JD, MB, TS, MPL, ML, LM, JG, WG, JR, MK, SE, IB, OK. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.969855/full#supplementary-material

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Zhang Jianglin,
Jinan University, China
Karanbir Brar,
University of Toronto, Canada

*CORRESPONDENCE
Hailong Lu
victor5769@126.com
Peisheng Jin
100000401006@xzhmu.edu.cn
Xianliang Yan
docyxl@163.com

†These authors have contributed equally to this work

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Palliative radiotherapy combined with stent insertion to relieve dysphagia in advanced esophageal carcinoma patients: A systematic review and meta–analysis

Zhiyuan Xu[1,2†], Haonan Liu[1,3†], Shengli Li[4†], Zhengxiang Han[3], Jingjing Chen[1,5], Xiangting Liu[1,6], Qiang Li[7], Hong Mu[8], Jiaqi Yuan[1,7], Hailong Lu[9*], Peisheng Jin[7*] and Xianliang Yan[2,10*]

[1]Xuzhou Medical University, Xuzhou, Jiangsu, China, [2]Department of Emergency, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [3]Department of Oncology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [4]Department of Medical Record Statistics, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [5]Department of Endocrinology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [6]General Practice, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [7]Department of Plastic Surgery, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [8]Follow-Up Office, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [9]Department of Gerontology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [10]Emergency Medicine Department, Suining People's Hospital, Xuzhou, China

Introduction: Esophageal cancer is one of the most aggressive malignancies with limited treatment options, thus resulting in high morbidity and mortality. For patients with advanced esophageal cancer, the median survival is 3–6 months, with the majority requiring intervention for dysphagia.

Objective: To compare the relief of dysphagia in patients with incurable esophageal cancer treated with stenting alone or a combination of stenting and palliative radiotherapy.

Methods: The protocol of this study was pre-registered on PROSPERO (CRD42022337481). We searched PubMed, Wan Fang, Cochrane Library, Embase, and Web of Science databases. The literature search, quality assessment, and data extraction were conducted by two reviewers independently. The primary endpoints included median overall survival and dysphagia scores. Bleeding events, stent migration, and pain events were secondary outcomes. The meta-analysis results (the primary and secondary outcomes) were pooled by means of a random-effect model or a fixed-effects model.

Results: Nine studies with a total of 851 patients were included in this meta-analysis, consisting of 412 patients in the stenting alone group and 439 patients in the palliative radiotherapy after esophageal cancer stenting (ROCS) group.

The ROCS group could significantly improve dysphagia scores (SMD: −0.77; 95% CI: −1.02 to −0.51) and median overall survival (SMD: 1.70; 95% CI: 0.67–2.72). Moreover, there were no significant differences between the two groups in bleeding events, pain events, and stent migration.

Conclusion: Patients with dysphagia in advanced esophageal cancer may benefit further from ROCS in median overall survival and dysphagia scores. However, there was no significant advantage in improving bleeding events, pain events, and stent migration. Therefore, it is urgent to find a better therapy to improve adverse events in the future.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42022337481.

KEYWORDS

dysphagia, stent, oesophagal cancer, radiotherapy, meta-analysis

Introduction

The incidence of esophageal cancer has rapidly increased over the past years, and it is currently the fifth most common type of cancer worldwide with a very high mortality rate (1–3). There were more than 604,000 people newly diagnosed with esophageal cancer and approximately 544,000 deaths due to esophageal cancer worldwide in 2020, according to the World Health Organization (WHO). A majority of patients present with an incurable disease and rapid progression. Patients with advanced esophageal cancer have a poor quality of life during their limited survival time because of dysphagia and have a median survival of 3–6 months. In addition, patients with advanced esophageal carcinoma had a poor quality of life during their limited survival time because of dysphagia.

The management of dysphagia owing to esophageal cancer is challenging. Several management options have been used for the palliation of dysphagia. As the search for ideal therapy for esophageal carcinoma continues, we focus on improvements in dysphagia, overall survival, and adverse events. This meta-analysis, therefore, aimed to evaluate the usefulness of palliative radiotherapy after esophageal cancer stenting (ROCS) for the treatment of patients with inoperable esophageal cancer. Then, it allows us to achieve a better knowledge of palliative modality treatment for advanced esophageal carcinoma patients. Several management options have been used for the palliation of dysphagia (4). Although chemical and thermal ablation, self-expanding metal stents (SEMS), and radiotherapy and chemotherapy alone or in combination were included as options to fight against esophageal cancer (2), placement of metal stents has been the current traditional intervention. However, stent placement is not complication-free (1, 2). Several randomized controlled trials (RCTs) have been performed to compare different treatments, but no one has shown significant advantages over the others.

Twenty years ago, attempts were adopted to combine radiotherapy with stent placement in patients with esophageal cancer (3). A few studies have reported superior results for ROCS with regard to both the relief of dysphagia and survival in patients with advanced esophageal cancer (5–8). Meanwhile, the risk of stent-related adverse events increases over time. Therefore, the guidelines published recently by the European Society of Gastrointestinal Endoscopy (ESGE) strongly summon palliative radiotherapy as a valid alternative to stenting in patients with dysphagia and longer life expectancy (3, 4).

Despite this strong recommendation, palliative radiotherapy is not fully utilized, possibly because of the unawareness of its usefulness (5, 9). ROCS is rarely used as a monotherapy for the rapid relief of dysphagia, but its use immediately after stenting has not been rigorously studied (2). At the same time, the choice of therapy remains a challenging issue due to individual patient factors that are of great complexity, such as age, tumor burden, baseline performance score, existence of metastases, and expected survival time (10).

Methods

This study was finished with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11) and was registered on PROSPERO successfully (CRD42022337481).

Data sources and search strategy

QL and HM conducted a comprehensive literature search to screen relevant full articles evaluating the efficacy of palliative radiotherapy combined with stent insertion to relieve dysphagia in advanced esophageal carcinoma patients.

We searched five electronic databases (PubMed, Wan Fang database, the Cochrane Library, Embase, Web of Science) from inception to 30 April 2022, with the following medical subject headings (MeSH) and keywords including "dysphagia," "stent OR Self-expandable Metallic Stent," "oesophageal cancer OR carcinoma," "inoperable esophageal carcinoma," "radiotherapy," and "brachytherapy." There were no language or date restrictions in this meta-analysis.

Inclusion/exclusion criteria

Eligible studies regarding patients with a diagnosis of dysphagia secondary to esophageal cancer treated by palliative radiotherapy combined with stent insertion were considered. ZX and JC independently applied the inclusion and exclusion criteria to the articles.

All the included studies met the following criteria:

1) RCTs or observational studies,

2) there were at least 30 patients in all selected studies,

3) the main interventions: patients with inoperable esophageal cancer treated with esophageal stenting alone or a combination of esophageal stenting and radiotherapy,

4) participants were adult (≥16 years old) patients with incurable esophageal carcinoma, and

5) studies included should report at least one of the predefined outcomes: dysphagia, survival, or complications (bleeding, pain, etc.).

The exclusion criteria included retrospective studies and prospective studies with less than 30 patients and studies published only in abstract form. Review articles, duplicate articles, editorials, and letters were excluded.

Study selection

Two review authors (XL and JC) independently scrutinized all studies by title and abstracts. A full-text review of all screened studies was then assessed to determine whether the studies fulfilled the inclusion criteria. Any disagreements were sorted out through discussion with all the authors.

Data extraction and study quality

Two reviewers (HNL and ZX) independently extracted the data from all included studies. Disagreements were resolved by discussion and consensus with the corresponding authors.

The authors used a standardized data extraction form containing the following items: first author, publication year, study characteristics (RCTs, retrospective and prospective studies), country, sample size, stent diameter, radiotherapy regimen, primary outcomes, the publication status, the study design and location, the number of centers involved, and the Score of the Newcastle Ottawa Quality Assessment Scale (NOS).

Risk-of-bias assessment

XL and JY assessed the risk of bias of the selected studies independently using the Cochrane risk-of-bias tool and the NOS. To assess the risk of bias within the included randomized trials, the methodological quality of potential studies was evaluated according to the Cochrane risk-of-bias tool (Figure 1).

The quality of observational studies was determined according to NOS. The difference in point of view was resolved by consulting the third researcher (XY).

Statistical analysis

We (SL and HNL) used the Stata Statistical Software (version 12.0; Stata Corp., College Station, TX, USA) and Review Manager (version 5.4; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) for all statistical analyses.

The primary and secondary outcomes were pooled by means of a random-effects model or a fixed-effects model (12). We integrated the dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous variables as standardized mean differences (SMDs) with 95% CI. Statistical heterogeneity was calculated by I2 tests, with I2 >50% being indicative of significant heterogeneity. The potential publication bias was assessed by visual inspection of Begg's funnel plot. Begg's rank correlation test and Egger's linear regression test were also evaluated at the $p < 0.10$ level of significance (13, 14). All tests were two-sided and a p-value less than 0.05 was considered statistically significant.

Results

Search results and trial characteristics

A total of 828 studies were identified through the systematic search. Eight hundred and twelve studies were

FIGURE 1
Risk bias assessment in the studies included.

excluded after screening the title and abstract, and 16 studies remained available. Seven articles were excluded for the following reasons: one article was related to duplicate data, one article did not include a control group, four articles did not provide relevant outcomes, and one article did not provide accurate experimental data. Nine studies with a total of 851 patients were included in the meta-analysis (Figure 2). The study characteristics are listed in Table 1. Of all nine studies, three studies were from Western countries (15, 17, 18), and six studies were from multiple areas (6, 16, 19–22). This meta-analysis included three RCTs (15, 16, 22) and six observational studies (6, 17–21). The sample size ranged from 34 to 220 patients. Median survival was the primary endpoint for most studies. A total of 851 patients were included in the meta-analysis, of which 439 patients were in the adjuvant external beam radiotherapy group and 412 patients were in the usual care alone group.

Median overall survival

Six studies (15–19, 22) provided data on the median overall survival. We found that ROCS had a significantly prolonged median overall survival compared with stenting alone (SMD: 1.70; 95% CI: 0.67–2.72). Significant heterogeneity was found among the six studies ($I^2 = 95.5\%$; $p < 0.001$) (Figure 3).

Dysphagia scores

Four studies (6, 16, 20, 21) provided data on the dysphagia scores. The data for the dysphagia scores were available in four articles. The pooled results indicated that patients receiving ROCS showed significantly better dysphagia scores than patients receiving stenting alone (SMD: −0.77; 95% CI: −1.02 to −0.51) with no significant heterogeneity ($I^2 = 40.3\%$; $p = 0.170$) (Figure 4).

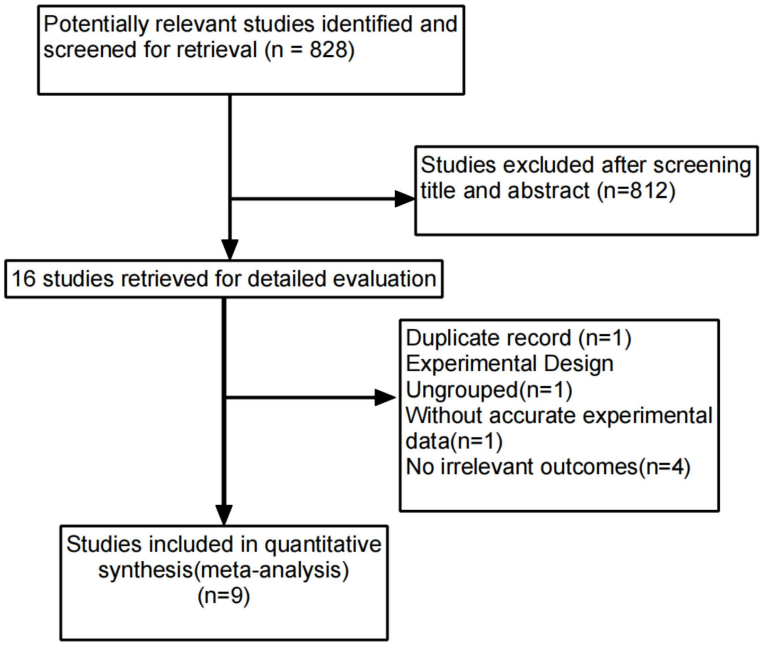

FIGURE 2
Process for identifying studies eligible for the meta-analysis.

Bleeding events

The data for bleeding events were extracted from four studies (6, 15, 19, 21). There was no significant difference in bleeding between the two groups (RR = 1.48; 95% CI: 0.63–3.49). No significant heterogeneity studies were observed between these studies (I2 = 27.6%; p = 0.246) (Figure 5).

Pain events

Five studies (6, 15, 18, 19, 21) presented data on pain events. The number of pain events was much the same between the ROCS group and the stenting alone group (RR: 1.10; 95% CI: 0.89–1.35). No heterogeneity was observed between studies (I2 = 42.1%, p = 0.141). Subgroup analysis was used to

TABLE 1 Summary of the identified nine studies.

Study	Year	Country	Research type	Sample size	Stent diameter (mm)	Radiotherapy regimen	Primary outcome	Scores of NOS	Scores of jaded
Adamson (15)	2021	UK	Randomized controlled study	220	Not given	20 Gy in five fractions or 30 Gy in 10 fractions	Median survival time	–	5
Javed (16)	2012	India	Randomized controlled study	84	18	30 Gy in 10 fractions	Median survival time	–	4
Eldeeb (17)	2012	UK	Prospective study	91	Not given	20 Gy in five fractions or 30 Gy in 10 fractions	Median survival time	8	–
Rueth (18)	2012	USA	Retrospective study	37	Not given	Not given	Median survival time	8	–
Song (19)	2002	China	Prospective study	108	16	Not given	Median survival time	7	–
Zhong (6)	2003	China	Prospective study	34	18	1.8 to 2.0 Gy for each session, 45 to 55 Gy totally	Dysphagia scores	6	–
Xie (20)	2002	China	Prospective study	47	Not given	1.8 Gy for each session, 45 to 55 Gy totally	Dysphagia scores	6	–
Ao (21)	2012	China	Retrospective study	150	Not given	2 Gy each time, 5 times a week	Dysphagia scores	7	–
Chen (22)	2009	China	Randomized controlled study	80	Not given	1.8 Gy for each session, 45 to 55 Gy totally	Median survival time	–	4

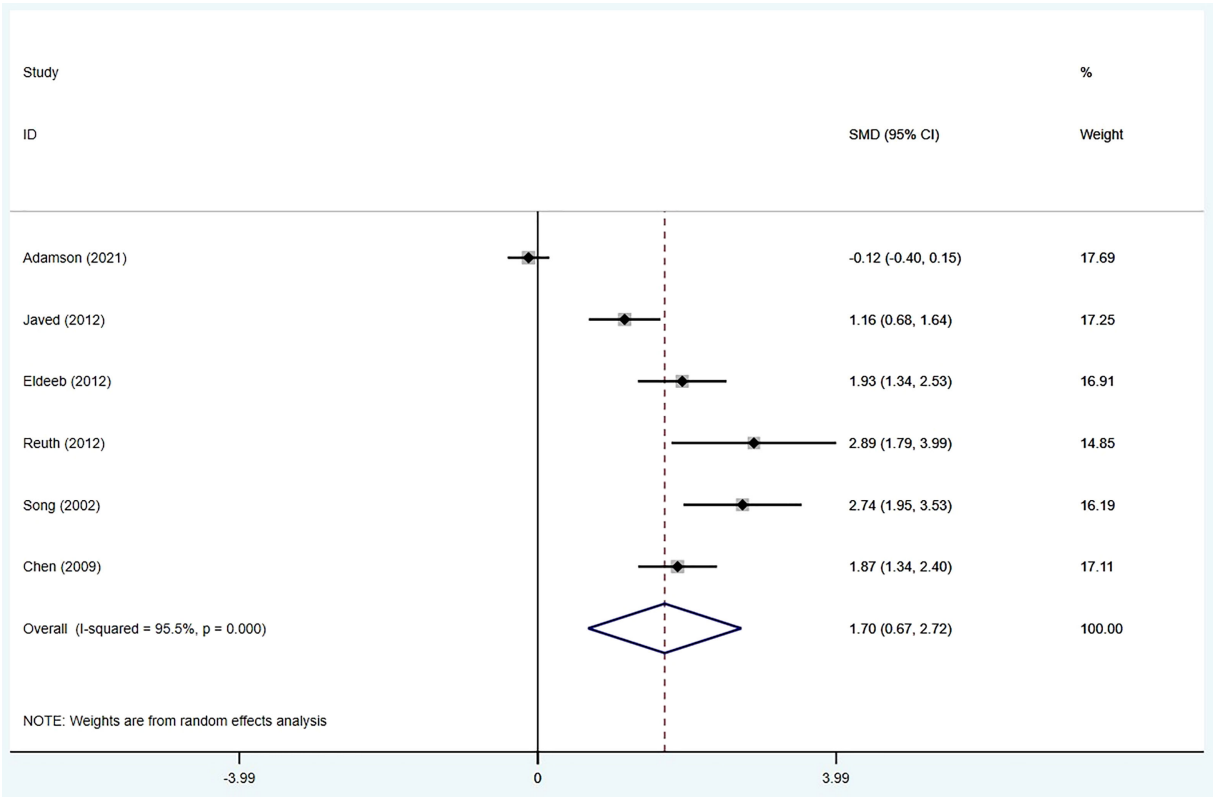

FIGURE 3
Forest plot for the results of median overall survival.

evaluate the RR of pain events based on different types of pain events. As shown in Figure 4, the RRs of stent-related pain and chest pain were 1.87 (95% CI: 0.87–4.02) and 0.97 (95% CI: 0.80–1.17), respectively (Figure 6).

Stent migration

Five of the study reports (6, 17–19, 21) revealed the data on stent migration. We discovered that there were comparable pooled stent migration events between the two groups (RR: 0.80; 95% CI: 0.41–1.87), and no significant heterogeneity was apparent among the five studies (I2 = 0.0%; p = 0.908) (Figure 7).

Publication bias

There was no evidence of publication bias by inspection of the funnel plot and statistical tests (Begg's test, p = 0.462; Egger's test, p = 0.118) (Figure 8).

Discussion

Of the nine trials included in this study, the clinical efficacies were primarily evaluated by comparing the median overall survival and dysphagia scores. Our results showed that ROCS can significantly improve median survival and dysphagia scores compared with the control group. However, ROCS group did not show significant improvement of related complications, such as bleeding events, stent migration, and pain events. In the majority of cases, the diagnosis of esophageal carcinoma occurs at an advanced stage (1). Despite the prevalence and impact of dysphagia in esophageal cancer, no systematic review has previously been attempted to summarize the evidence for palliative radiotherapy combined with stent insertion to relieve dysphagia in advanced esophageal carcinoma patients. Dua (2) found that esophageal stents were a very effective treatment for relieving dysphagia, with an effective rate of 96% to 100%. In this meta-analysis, we appraised the reported clinical efficacies of palliative radiotherapy after ROCS for treating patients with dysphagia in advanced esophageal carcinoma.

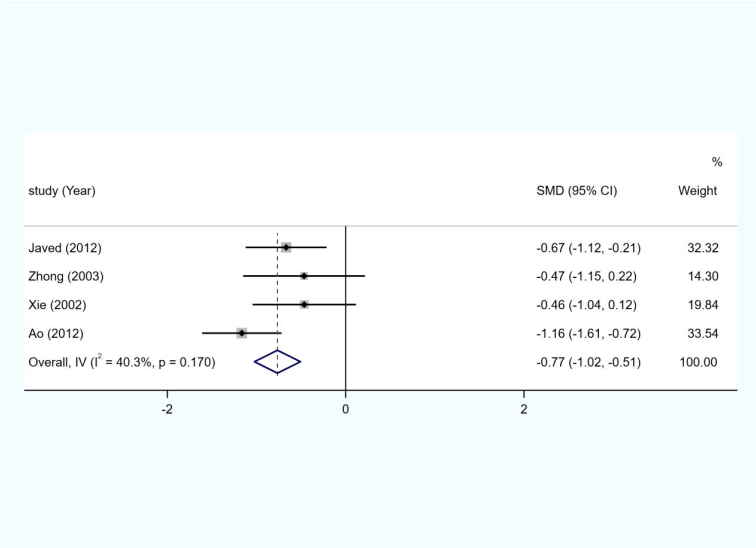

FIGURE 4
Forest plot for the results of dysphagia scores.

The first-line treatment option is generally represented by stent placement because of the simplicity of this procedure and the prompt resolution of dysphagia after stent deployment, which is achieved in almost all cases within 2 days (1). Stent placement is not complication-free, and the overall incidence of severe adverse events seems to be comparable to that of palliative ROCS (3). The efficacy of stenting tends to decrease over time; therefore, the most recent international guidelines recommend brachytherapy for patients with longer life expectancy (i.e., >4 months) (5, 23). The role of ROCS remains controversial. Indeed, in the study by Sur et al. published in 2004, the authors did not report any significant difference concerning the dysphagia-free survival (DFS) at 6 and 12 months after treatment between the groups receiving either stent alone or ROCS (10), while the study by Rosenblatt et al., published in 2010, showed a significant improvement of the DFS in the group of patients treated by ROCS (24). Therefore, the role of stent alone or ROCS in dysphagia in advanced esophageal carcinoma patients is still not clear, and further studies should investigate this issue. It is worth noting that substantial heterogeneity in the initial palliative approach of patients with inoperable esophageal cancer has been described (14, 25). The paucity of therapeutic guidance is possible to bring about this diversity in the initial treatment; indeed, clinical decision-making should be based not just on patient- and disease-related factors, but it should also be significantly influenced by the

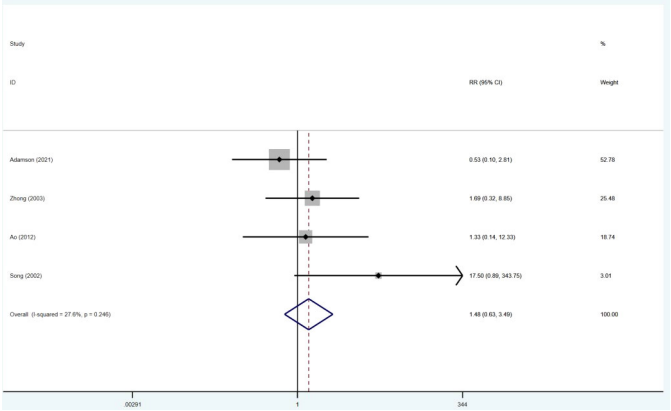

FIGURE 5
Forest plot for the results of bleeding events.

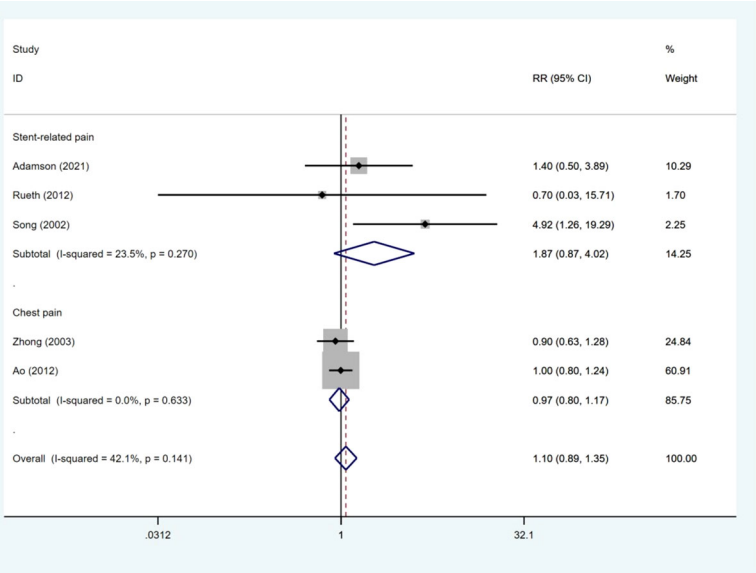

FIGURE 6
Forest plot for the results of pain events.

hospital of diagnosis (25). Therefore, governments and hospitals should strongly encourage evidence-based treatments and logistical issues contextually resolved to provide the optimal palliative management strategy.

The strengths of this study involved broad inclusion criteria and relevant exclusion criteria to ensure that all relevant studies were included in the review. Our study not only included relevant research on a global scale but also evaluated the relevant projects in strict accordance with the screening criteria corresponding to the topic. Nonetheless, everything has two sides. First, our meta-analysis presented with a considerable number of limitations, involving the heterogeneity of results, due to limited availability of information since only 9 studies were reviewed. Second, in order to pursue the universality of relevant research, some related studies included were conducted long ago, and the

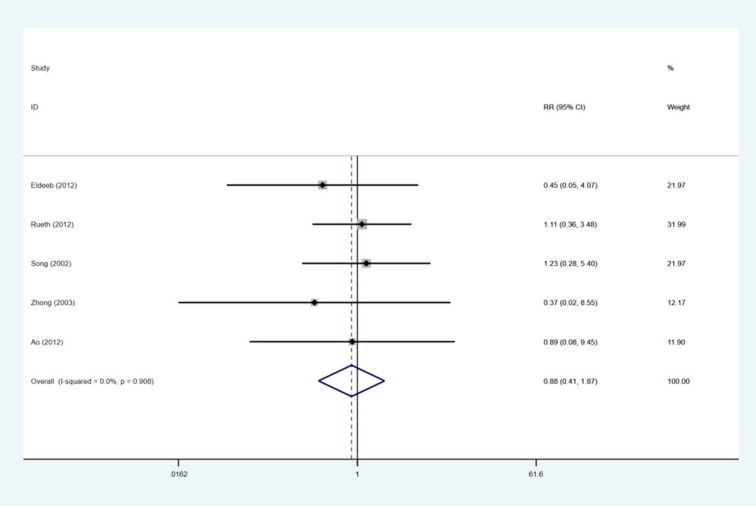

FIGURE 7
Forest plot for the results of stent migration.

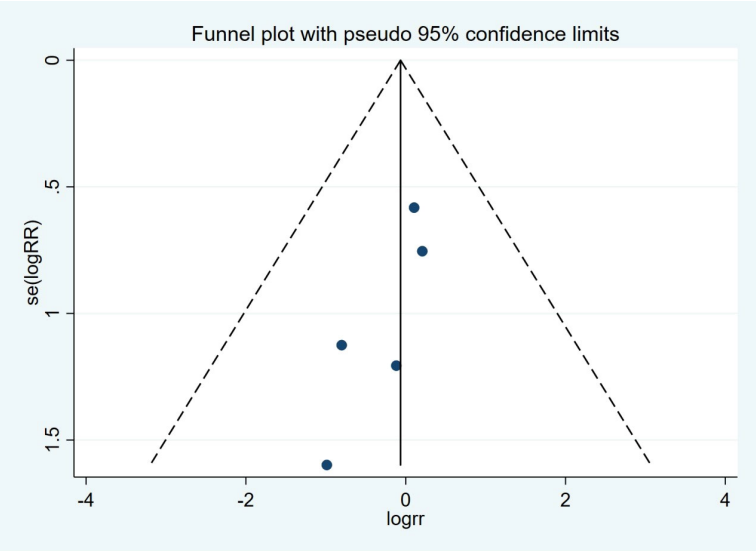

FIGURE 8
Funnel plots for stent migration.

quality of evidence for long interval studies comparing stent combination versus stenting alone was also very low, which may increase the heterogeneity of our results. Third, due to the complexity of the work and the diversity of the included studies, we did not conduct further analysis according to subgroups, and the patients included in the study had different follow-up years and distinct countries and nationalities, which further increased the heterogeneity of the results. Fourth, different treatment methods may also increase the heterogeneity of the research results. For example, in these projects included in our study, the doses and cycles of radiotherapy were not exactly the same. Fifth, different types of stent treatment may also have an impact on the results of the study, such as the material of the stents, the shape of the stents, the diameter of the stents, and so on. Sixth, there are wide confidence intervals for the pooled analyses of adverse events, which highlighted the lack of event data to draw meaningful conclusions. Above all, the types and sizes of esophageal tumors may affect the median survival time and complications after treatment, and subgroup analysis was not conducted in our study due to their diversity.

Conclusion

In conclusion, our meta-analysis demonstrated that patients with advanced esophageal cancer might benefit further from ROCS in median overall survival and dysphagia scores. However, there was no significant advantage in improving bleeding events, stent migration, and pain events. Future research should focus on combined therapy, which can alleviate adverse events. It is of great desirability that more RCTs are conducted to confirm the effects of the two groups of treatment.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Author contributions

ZX and HL: writing of this paper and collection of related research literature. JY, JC, and XL: extraction and proofreading of relevant data. QL and HM: supervision and improvement of article language quality. SL: guidance and supervision of statistical methods. PJ and XY: design of this study as well as funding support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Giuseppe Zimmitti,
Fondazione Poliambulanza Istituto Ospedaliero, Italy
Yoshihiro Ono,
Cancer Institute Hospital of Japanese Foundation for Cancer Research, Japan

*CORRESPONDENCE
Menghua Dai
daimh@pumch.cn
Yupei Zhao
zhao8028@263.net

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The effect of minimally invasive or open radical antegrade modular pancreatosplenectomy on pancreatic cancer: A multicenter randomized clinical trial protocol

Menghua Dai[1*], Hanyu Zhang[1], Yinmo Yang[2], Dianrong Xiu[3], Bing Peng[4], Bei Sun[5], Feng Cao[6], Zheng Wu[7], Lei Wang[8], Chunhui Yuan[3], Hua Chen[5], Zheng Wang[7], Xiaodong Tian[2], Hangyan Wang[3], Wenjing Liu[1], Jianwei Xu[8], Qiaofei Liu[1], Yupei Zhao[1*] and MIRROR study group

[1]Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China, [2]Department of General Surgery, Peking University First Hospital, Beijing, China, [3]Department of General Surgery, Peking University Third Hospital, Beijing, China, [4]Department of Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu, China, [5]Department of Pancreatic and Biliary Surgery, The First Affiliated Hospital of Harbin Medical University, Harbin, China, [6]Department of General Surgery, Xuan Wu Hospital, Capital Medical University, Beijing, China, [7]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [8]Department of Pancreatic Surgery, General Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Background: Radical antegrade modular pancreatosplenectomy (RAMPS) has been proven to improve R0 resection and lymph harvest in treating patients with distal pancreatic cancer. The development of minimally invasive surgery has advantages in postoperative recovery. Therefore, minimally invasive (MI-) RAMPS may combine the advantages of both benefits to improve survival. Nevertheless, evidence to validate the safety and efficacy of MI-RAMPS is limited.

Method/Design: The MIRROR trial will be the first multicenter prospective randomized clinical trial to investigate the outcome of MI-RAMPS. The hypothesis is that MI-RAMPS is superior in postoperative recovery. The primary outcome is the length of postoperative stay. Based on the hypothesis and primary outcome, the sample size is 250 patients (125 participants in each group). The trial will investigate factors related to surgical safety, short-term outcome, pathological assessment, and survival as secondary outcomes.

Conclusion: This study will offer a relatively higher level of evidence to further illustrate the accessibility and benefits of MI-RAMPS for the treatment of distal pancreatic cancer.

Clinical Trial Registration: Clinicaltrials.gov, NCT03770559.

KEYWORDS

clinical trial, design, pancreatic cancer, radical antegrade modular pancreatosplenectomy, minimally invasive surgery, length of stay, protocol

Introduction

Distal pancreatic cancer is a poorly-diagnosed disease with the highest incidence-to-mortality ratio worldwide (1, 2). The high incidence-to-mortality ratio is mainly due to delayed diagnosis, which limits treatment efficacy and options (3). Most recent consensus and guidelines recommend surgical resection if the primary tumor is resectable or borderline-resectable after neoadjuvant chemotherapy (3, 4). However, conventional distal pancreatosplenectomy (CDPS), which was recommended as one of the standard procedures for distal pancreatic cancer, has been reported to have unsatisfactory oncological outcomes in patients in recent years (5–7).

Accordingly, Strasberg et al. proposed radical antegrade modular pancreatosplenectomy (RAMPS) as one of the improved procedures for distal pancreatic cancer (8, 9). When compared with CDPS (5, 7, 10, 11), the procedure does not increase perioperative risks. Additionally, the expanded clearance of RAMPS results in better R0 resection rates and lymph node retrievals than CDPS. Therefore, compared with CDPS, RAMPS has been proven to be a safe procedure with better survival for patients with pancreatic cancer.

In the era of enhanced recovery surgery, minimally invasive surgery (MIS) has been widely accepted in the treatment of the most benign or low malignancy neoplasms of the pancreas (12). Nevertheless, the applicability of MIS in treating pancreatic cancer is controversial. The surgical outcomes and oncological safety of open and MIS procedures are of great interest among pancreatic surgeons. On the one hand, MIS is considered to result in less pain and shortened recovery time for the following anti-cancer treatments (13, 14). On the other hand, some malignant pancreatic cancer removals, such as RAMPS particularly, often have expanded surgical areas with the potential of more aggressive resection (8, 9).

In a previous study, we reported that the RAMPS cohort had a higher survival rate than the CDPS cohort (15). Subsequently, we performed a retrospective comparison between minimally invasive RAMPS (MI-RAMPS) and open RAMPS and found that MI-RAMPS is safer and has the potential advantages of faster recovery (16). Nevertheless, no prospective randomized clinical trial on the advantages of MI-RAMPS has been conducted. Therefore, the MIRROR study aims to conduct a multicenter, randomized controlled study to compare MI-RAMPS and open RAMPS (O-RAMPS) in treating patients with distal pancreatic cancer. This study will offer higher level evidence to pancreatic surgeons on the optimal use of MI-RAMPS to improve patients' postoperative recovery and combine with neo-/adjuvant therapy for better survival.

Method

Design

The MIRROR trial is a randomized controlled, parallel-group, multicenter, superiority trial investigating and comparing the safety and effect of MI-RAMPS and OP-RAMPS for pancreatic cancer (Figure 1). Eligible patients will be randomly assigned to either the MI-RAMPS or O-RAMPS treatment group. This trial protocol is based on the SPIRIT guidelines and checklist (17).

Study population

This study involves eight high-volume pancreatic surgery centers in China. Each participating center has performed >200 MI/O-RAMPS cases. All patients with suspected left-sided pancreatic cancer visiting outpatient clinics of these centers will be thoroughly evaluated according to the inclusion and exclusion criteria of the study.

Inclusion criteria

The inclusion criteria include (i) age ≥18 years; (ii) high suspicion or pathological diagnosis of pancreatic malignancy; (iii) resectable or borderline resectable tumor before surgery, regardless of neoadjuvant chemotherapy history; and (iv) eligibility for both MI-RAMPS and O-RAMPS based on evaluation by surgeons and anesthetists before surgery.

Exclusion criteria

The exclusion criteria include (i) suspicion or evidence of any distant metastasis or NCCN-defined unresectable arterial invasion; (ii) ASA physical status score ≥4; (iii) patient preference for a certain approach or change of willingness; and (iv) absence of malignancy based on the postoperative pathological report.

Borderline resectable tumor

According to NCCN version 1.2020 guidelines and Isaji et al. (18), a tumor will be classified as borderline resectable if at least one of the following factors is recognized: (i) Solid tumor contact with the superior mesenteric artery ≤180° or >180° without the involvement of the aorta and intact uninvolved gastroduodenal artery; (ii) solid tumor contact with the superior mesenteric vein or portal vein of >180° or contact ≤180° with contour irregularity or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction; (iii) carbohydrate antigen 19-9 (CA19-9) level >500 U/ml; and (iv) ECOG (19) performance status ≥2.

Although patients with borderline resectable tumors will be referred to an oncologist or multi-disciplinary team and recommended for neoadjuvant therapy, this situation will not be an independent factor for exclusion.

Randomization

Eligible participants will be recruited from eight centers after providing written informed consent. Stratified blocked randomization between O-RAMPS and MI-RAMPS will be performed in a 1:1 ratio; Before randomization, patients will be assigned to two subgroups based on resectability: borderline resectable subgroup and resectable subgroup to perform independent stratified randomization. Patients identified as borderline resectable, as illustrated in "borderline resectable tumor," will be assigned to borderline resectable subgroups. Otherwise, the case will be in the resectable group for randomization. The block sizes will be subjected to random variation. Randomization will be concealed from all investigators. Patients will be assigned codes by numeric randomization coding, and the study coordinator will be the only one with access to these codes. The source data will be stored digitally and kept in the central database. Randomization will be performed after the surgical plan is made and the written informed consent from patients and approval for the trial are available. Patients who rescind their decision to undergo surgery and those who do not undergo surgery will be excluded from the analysis.

Surgical technique

The RAMPS procedure is based on a report by Strasberg et al. (8, 9). All surgeons and their surgical teams are skilled in performing this procedure. To optimize for the best outcome, surgeons can decide to perform anterior or posterior RAMPS based on their evaluation of certain clinical cases during the surgery. Meanwhile, tiny variations in lymph node dissection and necessary extended tissue or organ resection, which are not beyond the guideline, are allowed (8, 9, 20, 21). In the MI-RAMPS group, all surgical teams can choose the appropriate general laparoscopic method or robotic techniques, such as the da Vinci® Surgical System, according to their preference and availability of resources.

Conversion

Conversion is defined as any case requiring additional hand-assisted approaches, except those for trocars and specimen collection, in the MI-RAMPS group (22, 23). Based on practical scenarios, the conversion will consist of reactive conversions (such as bleeding and organ perforation) and conditional conversions (such as difficult exposure, failure to proceed, and expanded tumor evasion) (22). The details about the conversion will be recorded for future analysis. According to the principle of intention-to-treat, patients who will undergo conversion will be continually analyzed in the MI-RAMPS group.

Blinding

The MIRROR trial is an open-label trial. However, several approaches will be applied to minimize the interference of subjective factors in the study findings. For example, patients will provide informed consent for both approaches and the study. However, they will be blinded to their specific groupings during the treatment. After the treatment, patients will not be actively informed of the specific surgical steps and procedures. The patient, however, reserves the right to know or quit anytime. Neither the pathologists involved in the postoperative evaluation nor the adjudication committee will be informed of treatment assignments.

General treatment regimen

The strategy and protocol of the general treatment during the perioperative period for both MI-RAMPS and O-RAMPS groups are the same. They include prophylactic drainage, nutritional support, anti-infection, proton pump inhibitor use, somatostatin use, blood sugar management, pain management, deep vein thrombosis prevention, and existing disease management. Other treatments, such as interventional therapy and reoperation, will be performed, if necessary, for the management of severe complications after the surgery.

Primary outcome

The primary outcome is the postoperative length of stay (LOS). Experienced surgeons will be responsible for the approval of discharge based on uniform criteria (24), including (i) no need for IV fluid; (ii) performance status and organ function recovery to the preoperative state; (iii) solid diet availability; (iv) no sign of infection; and (v) acceptable incision healing and pain control. However, discharge criteria do not include prophylactic drainage removal.

Patient evaluation will be recorded on case report forms (CRF) based on the observation and medical records for every round. Once the patient is eligible for discharge, the investigator will record the condition and date for the calculation of LOS, regardless of the similarity of the actual discharge date, as it may be affected by certain non-medical factors. If the evaluation for some cases is controversial, the senior surgical adjudication committee will be consulted.

Secondary outcomes

The secondary outcomes of the MIRROR study include surgical outcomes, complications, pathological outcomes, time and rate of return to adjuvant therapy, and long-term survival.

Surgical outcomes and complications

The details during the surgery will be recorded, including procedure type, surgical team, surgery duration, estimated blood loss, transfusion, conversion, combined vessel, and/or organ resection. To evaluate the quality of life, the VAS score, QLQ-C30, and QLQ-PAN26 will be used postoperatively.

Additionally, the rate of major complications and their detailed management will be recorded and investigated. Major complications will be defined according to the Clavien-Dindo grade III-IV classification system (25). Common complications after pancreatic surgery, such as postoperative pancreatic fistula, delayed gastric emptying, and hemorrhage, are classified based on the International Study Group on Pancreatic Surgery (ISGPS) guidelines (26–29). Only Grade B and C pancreatic fistula will be identified.

Pathological outcomes

All specimens will be collected for lymph node sorting, incision margin marking, and labeling by surgical team members (under the supervision of seniors or operators) and then sent to two pathologists for evaluation. R0 resection rate is one of the crucial secondary factors. R0 resection is recognized when the distance between the margin and tumor is >1 mm. R0 resection will be mainly evaluated using either the transection margin or retroperitoneal margin. Multiple pathological factors, such as the number of lymph node harvests, number of positive LN, LN ratio, and status of margin, will be recorded and analyzed if detectable (30). TNM staging according to the American Joint Committee on Cancer (AJCC) classification (8th edition) will be recorded (31).

Long-term survival

Disease-free survival (DFS) and overall survival (OS) will be used as secondary outcomes of this study. DFS is the postoperative survival period without recurrence and metastasis of the primary tumor. OS is defined as the entire length of survival after the RAMPS procedure. All related survival information, including recurrence, metastasis, and survival status, and the subsequent anti-cancer treatment information will be acquired during the postoperative follow-up. The anticipated mean follow-up period for the survival study is 24 months.

Patient follow-up

The follow-up plan consists of out-patient clinic visits 1, 3, and 6 months after the surgery. Thereafter, patients will be followed up every six months. In case of a no-show in the clinic, the interview by phone will be conducted at every interval. Detailed information on symptoms, lab tests, medical imaging examinations (ultrasound, CT, MRI, or PET-CT), adjuvant therapy regimen, recurrence, metastasis, and survival status will be recorded at every follow-up visit.

Data collection

All data of enrolled patients will be gathered into a central database, the Electronic Data Capture (EDC) system, based on

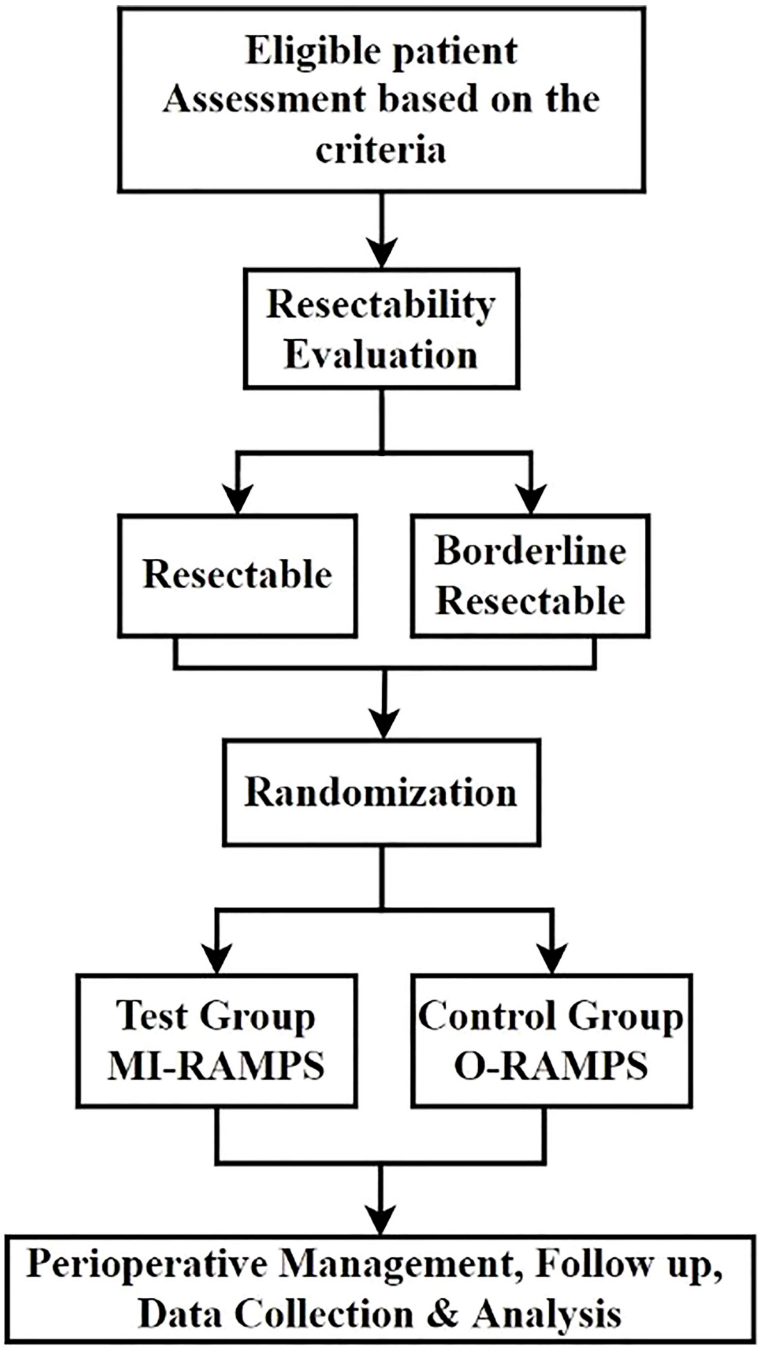

FIGURE 1
Study flowchart of MIRROR study.

the previous design of the CRF, which consists of baseline information, randomization result, lab test result, medical examination, surgical treatment information, peri-operative management record, and follow-up data. To secure quality and confidentiality, all data will be under surveillance by a third-party professional data management team.

Quality and safety

All participating centers and their surgical teams are experienced in RAMPS procedures and other pancreatic surgical procedures. Each center has at least one senior surgeon who will join the surgical adjudication committee,

comprising seniors from other centers, to ensure safety and procedure standards. All the senior surgeons are specialists in pancreatic surgery and will be available for assessment and consultation for difficult cases during the trial.

Regarding histopathological evaluation, all specimens, including primary tumor and resected lymph nodes, will be collected and marked (such as resection margin) by the surgical team before transfer to the pathological team. At least two expert pathologists will evaluate every case, one being a senior specialist in hepatopancreatobiliary (HPB) disease diagnosis. If the assessment is inconsistent with that of the other pathologist, another HPB pathologist will be invited for final evaluation.

Ethics

This trial will be conducted according to the principles of the Declaration of Helsinki (32). The study protocol has been received and approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital (No. ZS-1823). Additionally, approval was obtained according to the local regulations of all participating centers. The trial has been registered on Clinicaltrials.gov (NCT03770559).

Statistics

Sample size calculation

The MIRROR trial has been designed as a superiority trial. We hypothesize that patients with distal pancreatic cancer who undergo MI-RAMPS have a shorter postoperative stay than those who undergo O-RAMPS. Based on our previous experience and related data on the retrospective cohorts (15, 16), the expected superiority in the length of stay in the MI-RAMPS group is 3 ± 8 days. These factors, 5% two-sided significance level (α), 80% power (1-β), and 10% drop-off rate, were considered in calculating the sample size. Accordingly, the expected sample size has been set at 250 patients (125 patients in each group).

Statistical analysis

Continuous variables will be expressed as means with standard deviation or median and compared using the independent samples T-test and Wilcoxon rank test. Categorical variables will be described as percentages and compared using the Pearson Chi-square test, continuity correction, or Fisher's exact test. Survival will be evaluated using both OS and DFS. Clinically considerable or significant variables based on univariate analysis will be included in multivariate analysis, which will be performed by Cox regression analysis. P-value <0.05 will indicate statistical significance.

Discussion

For resectable and borderline resectable distal pancreatic cancer, one of the main goals of surgical treatment is the complete removal of the tumor and potentially involved tissues or organs, in addition to a necessary lymph node harvest. This approach is beneficial for the patient in reducing tumor burden and preventing recurrence and metastasis (3, 4). Furthermore, satisfactory lymph node dissection can improve the accuracy of TNM staging (33). In this regard, CDPS is currently considered limited by its ability to achieve appropriate oncological safety. Therefore, RAMPS surgery is widely known to improve R0 resection rate and lymph node dissection, thereby providing a better treatment strategy for distal pancreatic malignancies. Since MIS has the advantages of less injury, less pain stimulation, and faster recovery, it may shorten the postoperative recovery period of patients with pancreatic cancer to facilitate necessary postoperative adjuvant therapy (5, 13). However, the current high-level evidence-based medicine mainly focuses on benign or low-grade malignant tumors treated by minimally invasive pancreatic surgery (34, 35). For the treatment of distal pancreatic cancer, only one protocol of an ongoing multicenter randomized controlled trial, DIPLOMA, has been published (36, 37). Nevertheless, its surgical procedure for treating pancreatic cancer is mainly based on CDPS, and the research design is a non-inferiority study on R0 resection of MIS. Therefore, the ability of MI-RAMPS to promote early recovery without compromising on safety should be investigated to improve survival.

In this trial, RAMPS will be performed using either the anterior or posterior approach according to the scope of surgical resection, which is mainly selected according to the intraoperative assessment of the chief surgeon. However, we stratified resectability before randomization because of significant differences in treatment strategy and prognosis between patients with resectable and borderline resectable tumors. A common criterion for assessing resectability is vascular invasion. However, Isaji et al. (18) have proposed certain biological criteria (CA19-9) and performance status evaluation, which have been adopted in this study. Moreover, the MIRROR trial will include a strict pathological evaluation system to reflect the oncological outcomes of MI-RAMPS. Concerning the pathology report evaluation, we will follow the margin evaluation system proposed by the Japan Pancreas Society (30) and TNM staging by AJCC to evaluate the margins, lymph nodes, and suspicious invasion in multiple dimensions to ensure the diagnostic accuracy of the pathology report.

The primary outcome of this study will be the length of postoperative hospital stay. LOS could directly and better reflect the period between operation and postoperative adjuvant therapy. In this study, all participating centers and their pancreatic surgical teams are well-experienced in both O-

RAMPS and MI-RAMPS, as well as general peri-operative management. Moreover, each center has assigned at least one senior pancreatic specialist to join the adjudication committee for supervision and consultation. Therefore, to a certain extent, we believe that based on accurate evaluation criteria, the results of the corresponding superiority of LOS will indicate that MI-RAMPS is beneficial for enhanced postoperative recovery. By validating this hypothesis, we expect to provide distal pancreatic cancer patients with a safe, minimally invasive way to get the tumor radical removal and receive the necessary postoperative adjuvant therapy timely for the best chance of survival.

The MIRROR study is the first multicenter prospective randomized clinical trial to investigate the safety and efficacy of MI-RAMPS surgery for pancreatic body and tail cancer. Admittedly, our study is not an international multicenter study, mainly due to concerns about large differences and deviations in the discharge time among each country's national medical insurance policies and medical systems. Sample size estimation was based on LOS retrospective data from the principal investigation center, which may not be suitable for international trials. However, the conclusions will be beneficial to the exploration of further international studies and provide a reference for the establishment of RAMPS discharge standards and subsequent adjuvant therapy indications. Certainly, we encourage and look forward to conducting an international multi-center randomized clinical trial based on the results of this study for further investigation into the safety and efficacy of MI-RAMPS.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The conduction of the present trial is subject to the principles of the Declaration of Helsinki31. The study protocol has been received and approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital (No. ZS-1823). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MD conceived the study. MD and HZ contributed to the design of the study protocol. HZ wrote the draft of the manuscript. All authors contributed to the details of the study design, revision, and evaluation of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Alberto Puccini,
Ospedale Policlinico San Martino IRCCS, Italy

REVIEWED BY
Jin Tung Liang,
National Taiwan University, Taiwan
Masamitsu Hatakenaka,
Sapporo Medical University, Japan

*CORRESPONDENCE
Zhang Li-Ze
drzhanglize@qdu.edu.cn

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Impact of adequate lymph nodes dissection on survival in patients with stage I rectal cancer

Peng-Lin Liu, Dan-Dan Wang, Cheng-Jian Pang and Li-Ze Zhang*

Department of Anorectum, The Affiliated Hospital of Qingdao University, Shandong, China

Background and Aims: The NCCN guidelines recommended an assessment of ≥ 12 lymph nodes (LN) as an adequate LN dissection (LND) for rectal cancer (RC). However, the impact of adequate LND on survival in stage I RC patients remained unclear. Thus, we aimed to compare the survival between stage I RC patients with adequate and inadequate LND.

Methods: A total of 1,778 stage I RC patients in the SEER database from 2010 to 2017 treated with radical proctectomy were identified. The association between ≥ 12 LND and survival was examined using the multivariate Cox regression and the multivariate competing risk model referenced to < 12 LND.

Results: Stage I RC patients with ≥ 12 LND experienced a significantly lower hazard of cancer-specific death compared with those with < 12 LND in both multivariate Cox regression model (adjusted HR [hazard ratio], 0.44, 95% CI, 0.29-0.66; $P < 0.001$) and the multivariate competing risk model (adjusted subdistribution HR [SHR], 0.45, 95% CI, 0.30-0.69; $P < 0.001$). Further, subgroup analyses performed by pT stage. No positive association between ≥ 12 LND and survival was found in pT1N0 RC patients (adjusted HR: 0.62, 95% CI, 0.32-1.19; $P = 0.149$; adjusted SHR: 0.63, 95%CI, 0.33-1.20; $P = 0.158$), whereas a positive association between ≥ 12 LND and survival was found in pT2N0 RC patients (adjusted HR: 0.35, 95%CI, 0.21-0.58; $P < 0.001$; adjusted SHR: 0.36, 95%CI, 0.21-0.62; $P < 0.001$).

Conclusions: The long-term survival benefit of adequate LND was not found in pT1N0 but in pT2N0 RC patients, which suggested that pT2N0 RC patients should be treated with adequate LND and those with inadequate LND might need additional therapy.

KEYWORDS

rectal cancer, proctectomy, lymph nodes dissection, cancer-specific survival, SEER

Introduction

Colorectal cancer is the third most frequently diagnosed cancer and the second leading cause of cancer death worldwide. Of these, an estimated 732,210 cases of rectal cancer (RC) will occur, and an estimated 339,022 people will die of RC in 2020 (1). Traditionally, the radical curative treatment for RC has been proctectomy, which involved lymph nodes (LN) dissection (LND). An assessment of a minimum of 12 LND (≥ 12 LND) is recommended in NCCN Guidelines Version 2.2022. The adequate LND will reduce the risk of metastatic LN residual, and then optimize locoregional control and tumor staging. For example, the node-negative pT1/pT2 RC patients with few LND might not be truly node-negative but rather understaging, the pN0 could be staged pN1, even pN2 with more LND (2–5). Moreover, the isolated tumor cells and micrometastasis in LN are considered the risk factors that could increase the rate of local recurrence and decrease the long-term survival of RC patients (6–8). Whereas local excision, which typically did not involve LND, was increasingly used in the treatment of stage I RC patients which helped to preserve the anus and reduce the morbidity and mortality resulting from radical proctectomy and further enhance the quality of life (9). According to the American Society of Colon and Rectal Surgeons, the criteria for local excision included pT1 stage, well-to-moderately differentiated, less than 3 cm diameter, less than one-third of the bowel lumen circumference, and the absence of lymphovascular or perineural invasion (10, 11). Local excision was increasingly used for the treatment of pT1N0 RC patients, and previous studies have confirmed the compare oncological long-term survival between these patients treated with local excision and radical proctectomy (9, 12). However, it was surprising that local excision was also increasingly used for the treatment of pT2N0 RC patients who did not meet the criteria of local excision (9, 12). Thus, the survival benefit of adequate LND should be questioned for the treatment of stage I RC patients. In addition, stage II RC patients (i.e., pT3N0M0) with < 12 LND are thought to place patients at higher risk, and an additional adjuvant therapy might be taken into consideration for these patients (13). However, the association between adequate LND and survival in pT1/pT2N0 RC patients remained unclear, and no additional therapy was recommended for these patients.

Therefore, in the present study, we identified stage I RC patients treated with radical proctectomy in the Surveillance, Epidemiology, and End Results (SEER) database and further evaluated the association between adequate LND (≥ 12) and survival with inadequate LND (< 12) as a reference, separately for pT1N0 RC patients and pT2N0 RC patients.

Materials and methods

Study design

This was a retrospective cohort study of patients in the SEER database from 2010 to 2017 with stage I RC treated with radical proctectomy. Informed consent or institutional review was not required for the analyses of patients collected because the SEER database is publicly available.

Patients

Patients' data were collected from the SEER database using the National Cancer Institute's SEER*Stat software (version 8.3.5; www.seer.cancer.gov). The detailed inclusion and exclusion criteria for stage I RC patients are shown in Figure 1. Patients were enrolled in 1) they were 18 years or older, 2) the histological type included adenocarcinoma, and mucinous adenocarcinoma, 3) they underwent radical proctectomy, 4) they had pT1/pT2N0M0 tumor, 5) they received no adjuvant therapy, 6) and they were actively followed up (follow-up time ≥ 1 month; known cause of death). Ultimately, 1,778 stage I RC patients with radical proctectomy were identified in the present study. The median follow-up time was 70 months, ranging between 46 and 94.

Variables and outcomes

Stage I RC Patients were classified into inadequate LND (<12) and adequate LND (≥ 12) groups according to the number of LN examined. The assessment of 12 LN was chosen as the landmark of adequate LND following the NCCN guidelines (13). Patients' demographic variables were age at diagnosis in 10-year increments, gender, and race (White, Black, and others). Tumor variables were pT stage (pT1 and pT2 stage), tumor grade (well/moderately differentiated and poor/anaplastic), tumor size (≤ 3 cm, > 3 cm, and unknown), CEA level (negative/unknown and positive) and perineural invasion (negative/unknown and positive).

Statistical methods

Differences in patients' demographics and tumor characteristics between inadequate LND and adequate LND were tested using the chi-square (χ^2) test or Fisher's exact test. The cancer-specific survival (CSS) was defined as RC's time from diagnosis to death. For the competing risk model, death was classified into two groups: death related to RC and death not related to RC, which was considered a competing risk event. Patients who were still alive

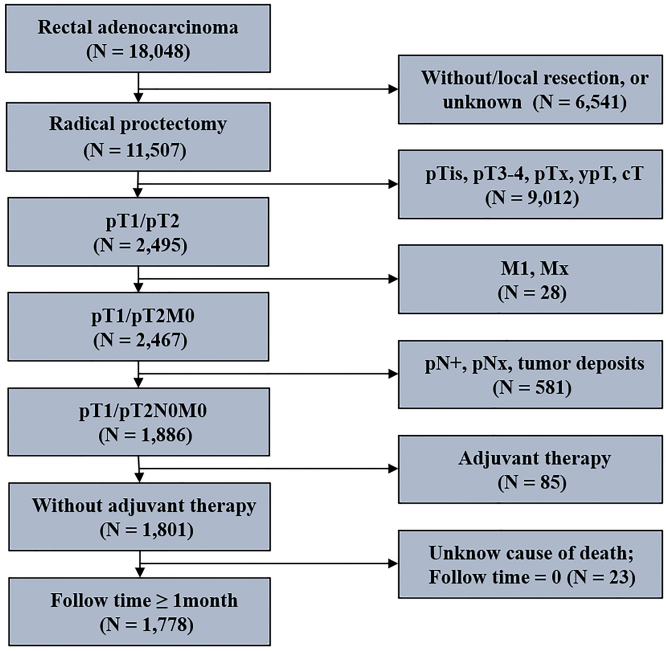

FIGURE 1
The flowchart of stage I rectal cancer patients included the process.

were censored at the date of the last contact. The CSS probabilities were calculated using the Kaplan-Meier method, and CSS probabilities differences between the groups were tested by the log-rank test. The multivariate Cox proportional hazards regression was performed to calculate the adjusted hazard ratio (HR) with 95% CI and evaluate the independent predictors of CSS. Taking into consideration the death not related to the RC, the competing risk model was performed to calculate the cumulative incidence of cancer-specific death (CSD) and the competing risk events, and the cumulative incidence differences between the groups were tested by the Gray's test. The multivariate Fine and Gray's competing risk regression model was performed to calculate the adjusted subdistribution HR (SHR) and 95% CI and evaluate the independent predictors of CSD (14). All statistical analyses were carried out using R statistical software (version 4.0.2, www.r-project.org). Two-sided P <.05 were considered statistically significant.

Results

Patients' demographics and tumor characteristics

As shown in Figure 1, 1,778 stage I RC patients with radical proctectomy were identified in the present study. Of these, 425 patients with < 12 LND, and 1,353 patients with ≥ 12 LND. Table 1 shows the differences in clinical characteristics between stage I RC patients with < 12 and ≥ 12 LND. Results showed that stage I RC patients with < 12 LND were diagnosed at an older age, with an earlier pT stage and a smaller size tumor compared with those with ≥ 12 LND. The differences in clinicopathological characteristics between patients with < 12 and ≥ 12 LND, separately for pT1N0 and pT2N0 RC patients, were summarized in Supplemental Table 1, 2. Similar results were found that pT1N0 or pT2N0 RC patients with < 12 LND were diagnosed at an older age and with a smaller size tumor compared with those with ≥ 12 LND.

The association between lymph nodes dissection and prognosis

Kaplan-Meier survival curves are shown in Figure 2A. The 5-year CSS rate was 93.0% (95% CI, 90.4%–95.7%) for stage I RC patients with < 12 LND, and 95.7% (95% CI, 94.5%–96.9%) for stage I RC patients with ≥ 12 LND. The log-rank test showed that stage I RC patients with ≥ 12 LND had significantly better CSS rates compared with those with < 12 LND (P < 0.001, Figure 2A). To adjust for potential confounding factors, a multivariate Cox regression model was performed. stage I RC patients with ≥ 12 LND experienced a significantly lower hazard

TABLE 1 Clinicopathological differences between stage I rectal adenocarcinoma patients with < 12 and ≥ 12 lymph nodes dissection.

Characteristic	TotalN = 1,778	< 12 lymph nodesN = 425	≥ 12 lymph nodesN = 1,353	*P-value*
Age of diagnosis (years)				0.006
< 50y	196 (6.0)	32 (7.5)	164 (12.1)	
< 60y	577 (32.5)	125 (29.4)	452 (33.4)	
< 70y	505 (28.4)	131 (30.8)	374 (27.6)	
≥ 70y	500 (28.1)	137 (32.2)	363 (26.8)	
Gender				0.065
Female	778 (43.8)	169 (39.8)	609 (45.0)	
Male	1,000 (56.2)	256 (60.2)	744 (55.0)	
Race				0.425
White	1,538 (86.5)	375 (88.2)	1,163 (86.0)	
Black	60 (3.4)	14 (3.3)	46 (3.4)	
Others	180 (10.1)	36 (8.5)	144 (10.6)	
pT stage				< 0.001
pT1	941 (52.9)	281 (66.1)	660 (48.8)	
pT2	837 (47.1)	144 (33.9)	693 (51.2)	
Tumor grade				0.292
Well/Moderately	1,544 (86.8)	373 (87.8)	1,171 (86.5)	
Poor/Anaplastic	142 (8.0)	27 (6.4)	115 (8.5)	
Unknown	92 (5.2)	25 (5.9)	67 (5.0)	
Tumor size				< 0.001
≤ 3cm	1,007 (56.6)	255 (60.0)	752 (55.6)	
> 3 cm	542 (30.5)	87 (20.5)	455 (33.6)	
Unknown	229 (12.9)	83 (19.5)	146 (10.8)	
CEA level				0.804
Negative/Unknown	1,620 (91.1)	389 (91.5)	1,231 (91.0)	
Positive	158 (8.9)	36 (8.5)	122 (9.0)	
Perineural invasion				0.663
Negative/Unknown	1,742 (98.0)	418 (98.4)	1,324 (97.9)	
Positive	36 (2.0)	7 (1.6)	29 (2.1)	

Values are n (%) unless otherwise defined.

of CSD compared with those with < 12 LND (adjusted HR, 0.44, 95% CI, 0.29–0.66; $P < 0.001$, Table 2).

Taking into consideration death not related to RC, the competing risk model was performed. The 5-year cumulative incidence of CSD rate was 6.6% (95% CI, 4.1%-9.1%) for stage I RC patients with < 12 LND, and 4.2% (95% CI, 3.0%-5.3%) for stage I RC patients with ≥ 12 LND. The Gray's test showed that stage I RC patients with ≥ 12 LND had significantly lower CSD rates compared with those with < 12 LND (P < 0.001, Figure 2B). Also, a multivariate Fine and Gray's competing risk regression model was performed to adjust for potential confounding factors. Stage I RC patients with ≥ 12 LND experienced a significantly lower hazard of CSD compared with those with < 12 LND (adjusted SHR, 0.45, 95% CI, 0.30-0.69; $P < 0.001$, Table 2).

Subgroup analyses were performed by pT stage. For pT1N0 RC patients, no positive association between ≥ 12 LND and CSS was found in the log-rank test (Five-year CSS: 97.1% *vs.* 96.4%, $P = 0.128$, Figure 3A) and the multivariate Cox regression model (adjusted HR: 0.62, 95%CI, 0.32-1.19; $P = 0.149$, Supplemental Table 3). Taking into consideration death not related to RC, no positive association between ≥ 12 LND and CSD was found in the Gray's test (Five-year CSD: 2.8% *vs.* 3.4%, $P = 0.144$, Figure 3B) and the multivariate Fine and Gray's competing risk regression model (adjusted SHR: 0.63, 95%CI, 0.33-1.20; P = 0.158, Supplemental Table 3). Conversely, a statistically significant survival benefit of ≥ 12 LND was found in pT2N0 RC patients in the log-rank test (Five-year CSS: 94.3% *vs.* 86.3%; $P < 0.001$, Figure 4A) and the multivariate Cox regression model (adjusted HR: 0.35, 95%CI, 0.21-0.58; $P < 0.001$, Supplemental Table 4). Also, taking into consideration death not related to RC, the statistically significant survival benefit of ≥ 12 LND did not change in pT2N0 RC patients in the univariate (Five-year CSD: 5.4% *vs.* 12.7%; $P < 0.001$, Figure 4B) and the multivariate competing risk model (adjusted SHR: 0.36, 95%CI, 0.21-0.62; $P < 0.001$, Supplemental Table 4).

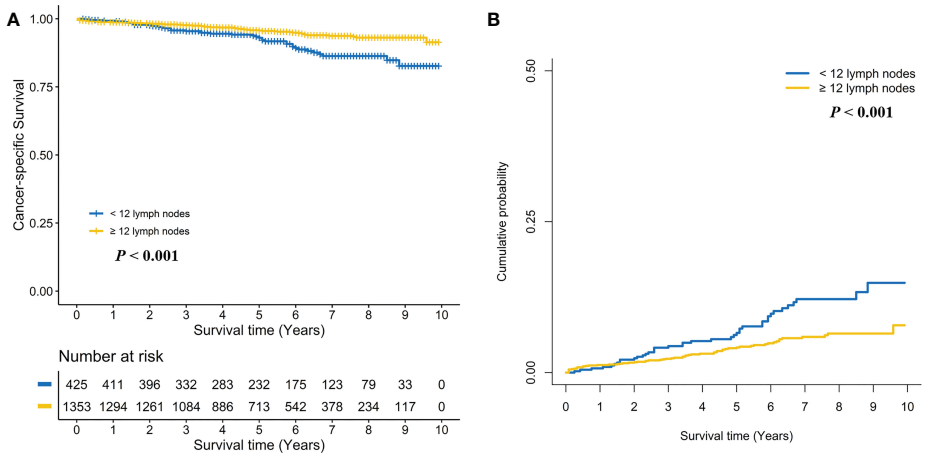

FIGURE 2
Comparison of cancer-specific survival **(A)** and cumulative probability of cancer-specific death **(B)** in stage I rectal cancer patients between < 12 and ≥ 12 lymph nodes dissection.

Additionally, we conducted sensitivity analyses to assess the robustness of our results by excluding patients whose follow-up time was ≤ 3 months to account for bias due to surgery-associated death (15). The ≤ 3 months mortality for stage I RC patients with < 12 LND was 1.38% (6/436), which was insignificantly lower compared with 2.11% (28/1329) for stage I RC patients with ≥ 12 LND (P = 0.456). Landmark survival analyses were performed, and the statistically significant survival benefit of ≥ 12 LND were found in the stage I RC patients in the log-rank test (Five-year CSS: 96.3% *vs*. 93.2%, P < 0.001, Supplemental Figure 1A) and the multivariate Cox regression model (adjusted HR, 0.39; 95% CI, 0.25-0.59; P < 0.001, Supplemental Table 5) with exposure starting at > 3 months. Taking into consideration death not related to RC, the statistically significant survival benefit of ≥ 12 LND was no change in the stage I RC patients in the Gray's test (Five-year CSD: 3.5% *vs*. 6.4%, P < 0.001, Supplemental Figure 1B) and the multivariate Fine and Gray's competing risk regression model (adjusted SHR, 0.39; 95% CI, 0.25-0.61; P < 0.001, Supplemental Table 5). We also performed the same sensitivity analyses for stage I RC patients by pT stage. No positive association between ≥ 12 LND and survival was found in pT1N0 RC patients (Supplemental Figures 2A, B; Supplemental Table 5), whereas a positive association between ≥ 12 LND and survival was found in pT2N0 RC patients (Supplemental Figures 3A, B; Supplemental Table 5).

Discussion

Traditionally, proctectomy along with adequate LND is the standard of surgical treatment for the vast majority of RC patients. The adequate LND will reduce the risk of metastatic LN residual and then optimize locoregional control and tumor staging. However, for pT1/pT2N0 RC patients, the association between adequate LND and survival remained unclear, and additional therapy was not recommended for these patients with < 12 LND. Thus, we need to evaluate the association between adequate LND and survival in pT1/pT2N0 RC patients.

In the present study, the long-term survival benefit of adequate LND was found in stage I RC patients. Further, subgroup analyses by pT stage suggested that the long-term survival benefit of adequate LND was not in pT1N0 RC patients but in pT2N0 RC patients. The main interpretation for that was the different risk of occult LN metastasis residual between pT1N0 and pT2N0 RC patients (2, 5). A previous study suggested that the incidence of radiographically occult LN metastasis ranges from 6% for low-risk T1 tumors to as high as 65% for poorly differentiated T2 tumors with lymphovascular invasion (LVI) (5). The survival benefit of adequate LND is correlated with the risk of occult LN metastasis residual. The occult LN metastasis residual will increase the risk of locoregional recurrence, which cannot all be amenable to salvage surgical therapy or multimodality therapy (16–18). Previous retrospective studies using the SEER database showed that the survival benefit of radical proctectomy (involved LND) was not found in pT1N0 RC patients but in pT2N0 RC patients referenced to local excision (not involved LND) (9, 12, 19). And the proctectomy can provide better regional control than local excision (LE) for early RC patients, especially for T2 patients (10, 13). Similarly, pT2N0 but not pT1N0 RC patients, will benefit from adequate LND in the present study, which also lent support to the local excision for the treatment of pT1N0 but not for pT2N0 RC patients. Thus, cautions were needed in expanding

TABLE 2 The predictors of survival for pT1/pT2N0 rectal cancer patients in both multivariate Cox regression model and the multivariate competing risk model.

	Cox regression model		Competing risk model	
Characteristic	**adjusted HR (95% CI)**	***P-value***	**adjusted SHR (95% CI)**	***P-value***
Age of diagnosis				
< 50y	Reference		Reference	
< 60y	0.83 (0.34, 2.01)	0.671	0.82 (0.33, 2.04)	0.673
< 70y	1.62 (0.70, 3.74)	0.259	1.61 (0.68, 3.84)	0.280
≥ 70y	2.64 (1.18, 5.88)	0.018	2.40 (1.06, 5.44)	0.036
Gender				
Female	Reference		Reference	
Male	0.99 (0.66, 1.47)	0.944	0.97 (0.64, 1.46)	0.885
Race				
White	Reference		Reference	
Black	2.25 (0.90, 5.64)	0.082	2.31 (0.95, 5.63)	0.066
Others	0.84 (0.41, 1.74)	0.643	0.87 (0.42, 1.78)	0.698
pT stage				
pT1	Reference		Reference	
pT2	1.85 (1.18, 2.91)	0.007	1.83 (1.15, 2.92)	0.011
Tumor grade				
Well/Moderately	Reference		Reference	
Poor/Anaplastic	1.37 (0.73, 2.57)	0.325	1.37 (0.72, 2.61)	0.330
Unknown	0.24 (0.03, 1.79)	0.166	0.24 (0.03, 1.88)	0.175
Tumor size				
≤ 3cm	Reference		Reference	
> 3 cm	0.89 (0.57, 1.39)	0.609	0.88 (0.56, 1.39)	0.586
Unknown	0.64 (0.28, 1.42)	0.271	0.63 (0.27, 1.44)	0.270
CEA level				
Negative/Unknown	Reference		Reference	
Positive	1.90 (1.13, 3.17)	0.015	1.85 (1.10, 3.11)	0.020
Perineural invasion				
Negative/Unknown	Reference		Reference	
Positive	0.49 (0.07, 3.58)	0.485	0.48 (0.07, 3.27)	0.456
Lymph node dissection				
< 12	Reference		Reference	
≥ 12	0.44 (0.29, 0.66)	< 0.001	0.45 (0.30, 0.69)	< 0.001

practice of LE in T2 patients, and adjuvant therapy might be needed for T2 patients treated with LE or proctectomy with inadequate LND. For cT1N0 patients, additional therapy might be needed for those were upstaged to pT2N0 after surgery and with inadequate LND. For cT2N0 patients, adequate LND would be needed.

However, local excision was increasingly used in the treatment of T2N0 RC patients (9, 12). The addition of chemoradiotherapy has been proposed to improve oncologic control (20–25). Previous studies have suggested that T2N0 RC had an equivalent survival between local excision plus adjuvant therapy and radical proctectomy (20–25). A recent study reported that cT2N0 RC treated with neoadjuvant chemoradiotherapy followed by local excision had a comparable survival to those treated with radical proctectomy (22). In the present study, pT2N0 RC patients with adequate LND had statistically significant higher CSS rates and lower CSD rates than those with < 12 LND, which suggested that these patients with < 12 LND were at higher risk, and an additional adjuvant therapy might be needed for these patients to improve oncologic control. However, the actual survival benefit of additional chemoradiotherapy remained unclear for pT2N0 RC patients with < 12 LND in the present study of the limited data. A previous study have indicated a small but statistically significant survival benefit of adjuvant therapy for stage II RC patients, and the benefit of adjuvant therapy is more significant

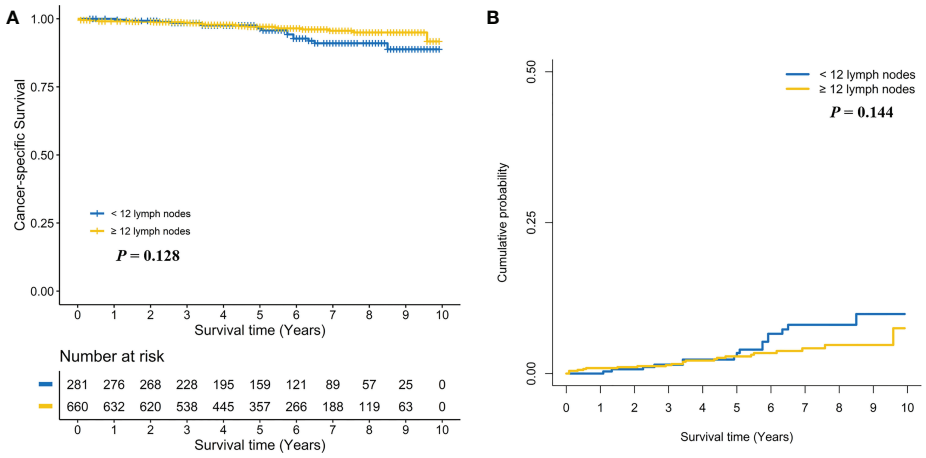

FIGURE 3
Comparison of cancer-specific survival **(A)** and cumulative probability of cancer-specific death **(B)** in pT1N0 rectal cancer patients between < 12 and ≥ 12 lymph nodes dissection.

in patients at high-risk, such as in patients with < 12 LND (26, 27). It is reasonable to infer that pT2N0 RC patients with < 12 LND can obtain better local control but a smaller survival benefit after adjuvant therapy referenced to stage II RC patients. Thus, decision-making regarding the use of adjuvant therapy for pT2N0 RC patients with < 12 LND should incorporate patient discussions individualized for the patient and should include the risk of occult nodal metastasis residual and the possible limited benefit and toxicities associated with additional therapy.

The present study with some limitations that should be noticed. Firstly, LVI and tumor budding, which are identified high-risk factors for LN metastasis, were not assessed in the SEER database (10, 11). RC patients with LVI and tumor budding received an inadequately sampled nodes were at higher risk of occult LN metastasis residual, which was associated with worse oncological survival. However, these patients will have a more aggressive LND, and most patients will be excluded in the present study for the positive LN. Previous study suggested that lymph-node distribution rather than number of LN metastasis is a valuable predictor of T1-2 colorectal cancer survival (28). However, the extent of LND was lacked in the SEER database. It was worth further study the

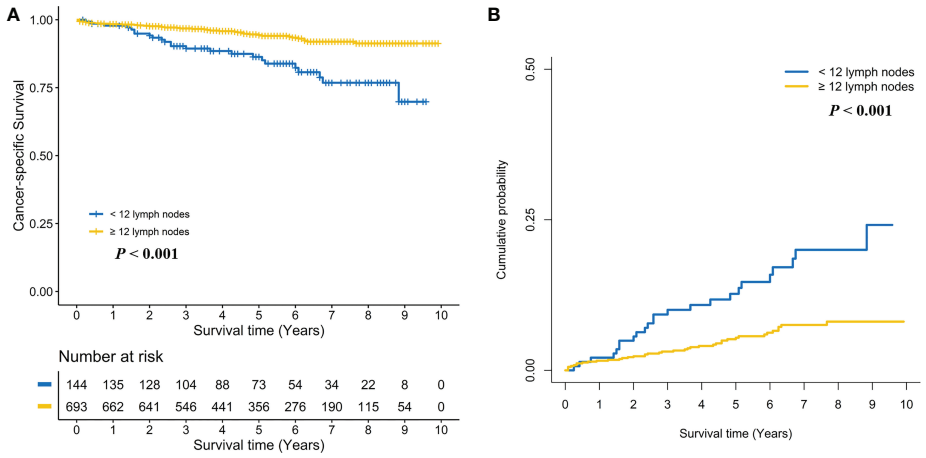

FIGURE 4
Comparison of cancer-specific survival **(A)** and cumulative probability of cancer-specific death **(B)** in pT2N0 rectal cancer patients between < 12 and ≥ 12 lymph nodes dissection.

prognosis value of the extent of LND, not only the number of LND, in pT1-2N0 RC patients. Secondly, resection margin status which is associated with local recurrence of cancer was also lacking in the database. However, most stage I RC patients with positive resection margin status would choose additional adjuvant therapy if they refused extended surgery, these patients were excluded in the present study. Thirdly, The SEER database also lacked data on the recurrence of cancer and salvage therapy procedures. However, it provides the cause of death to calculate CSS, which is correlated chronologically with cancer recurrence and salvage therapy procedures. Lastly, the nature of the retrospective study. Patient groups were nonrandomized, leading to a selection bias. The imbalance of patients' demographics and tumor characteristics was found between stage I RC patients with inadequate and adequate LND. Also, significantly different cumulative incidences of competing events were found between stage I RC patients with inadequate and adequate LND in the present study. The inherent selection bias could only be minimally controlled using the multivariable model.

Conclusions

Despite the limitations and inherent selection bias of retrospective study, this study demonstrated the long-term survival benefit of adequate LND in stage I RC patients. Further subgroup analyses found that the long-term survival benefit of adequate LND was not in pT1N0 but in pT2N0 RC patients. Decision-making regarding the use of adjuvant therapy for pT2N0 RC patients with inadequate LND should balance the possible limited survival benefit against toxicities associated with additional therapy.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LP-L, WD-D, PC-J, and ZL-Z participated in the design of this project, interpretation of data, drafting, and critical revision of the article, and provided final approval of the version to be submitted. LP-L and ZL-Z completed the data collection and analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.985324/full#supplementary-material

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Shucai Yang,
pingshan district people's hospital, China
Shixiong Liang,
Guangxi Medical University Cancer Hospital, China

*CORRESPONDENCE
Shizhong Yang
ysza02008@btch.edu.cn
Gong Li
lga02375@ btch.edu.cn
Jiahong Dong
dongjiahong@mail.tsinghua.edu.cn

†These authors have contributed equally to this work and share first authorship

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Safety and efficacy of radiotherapy combined with lenvatinib plus PD-1 inhibitors as neo-adjuvant therapy in hepatocellular carcinoma with portal vein thrombus: protocol of an open-label, single-arm, prospective, multi-center phase I trial

Guangxin Li[1†], Bin Shu[2†], Zhuozhao Zheng[3], Hongfang Yin[4], Chen Zhang[3], Ying Xiao[4], Yanmei Yang[1], Zhe Yan[2], Xiaofei Zhang[5], Shizhong Yang[2*], Gong Li[1*] and Jiahong Dong[2,6*]

[1]Department of Radiation Oncology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [2]Hepatopancereatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [3]Department of Radiology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [4]Department of Pathology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [5]Center for Clinical Epidemiology & Biostatistics, Beijing Tsinghua Changgung hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [6]Research Unit of Precision Hepatobiliary Surgery Paradigm, Chinese Academy of Medical Sciences, Beijing, China

Background: Surgical resection is a mainstay to treat hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) in east Asia. However, the postoperative recurrence rate is high. It is necessary to explore neo-adjuvant therapy to increase the surgical resection rate and improve overall survival. Evidence has shown that lenvatinib combined with PD-1 inhibitors is safe and effective in the treatment of advanced unresectable HCC. Radiotherapy is also an effective treatment method for PVTT and has a synergistic effect in combination with PD-1 inhibitors. Surgical resection after Lenvatinib and sintilimab combined with radiotherapy as a neoadjuvant treatment regimen may be a new exploration of HCC with PVTT, but there were not any reported.

Methods: This open-label, single-arm, prospective, multi-center Phase I trial will enroll 20 HCC patients with PVTT who have a resectable primary tumor and no extra-hepatic metastasis. Eligible patients will be given radiotherapy, 3Gy*10 fraction, and will receive lenvatinib 8-12mg once daily and sintilimab 200mg once every three weeks. Surgical resection will be performed 6-8 weeks after

radiotherapy. The primary endpoint is safety (number of patients ≥3G TRAE) and the number of patients who complete pre-op treatment and proceed to surgery. The secondary study endpoints include Major Pathological Response (MPR), 1-year tumor recurrence-free rate, Objective Response Rate (ORR), Imaging-Pathology Concordance Rate (IPCR), PVTT regression rate, Median Overall Survival (OS) and Recurrence Free Survival (RFS).

Discussion: This trial may confirm that surgical resection following intensive neoadjuvant therapy can provide a safe and efficient regimen for BCLC stage C patients with PVTT.

Clinical trial registration: https://clinicaltrials.gov/, identifier (NCT05225116).

KEYWORDS

radiotherapy, lenvatinib, sintilimab, HCC, PVTT

Introduction

Portal vein tumor thrombus (PVTT), having biological behavior of vascular invasion, is common in patients who are first diagnosed with hepatocellular carcinoma (HCC). The incidence of PVTT varies between countries and regions, ranging from 13% to 45% (1). HCC patients with PVTT have a worse prognosis, with a median survival of only 4-6 months given the best supportive care (2, 3). The management guidelines of HCC in the United States and ESMO recommend sorafenib and Lenvatinib as first line systemic therapy for PVTT patients (4, 5). However, the efficacy is modest. Guidelines for the management of HCC in Asia, such as Asian-Pacific guidelines (6) and guidelines in mainland China (7), Korea (8), and Taiwan (9), suggest that local therapies (hepatic resection, radiotherapy, TACE, and HAIC for example) are optional regimen for patients with PVTT. A real-world study in Japan reported postoperative recurrence-free survival according to the degree of PVTT as follows: Vp1, 1.23 years; Vp2, 0.82 years; Vp3, 0.56 years and Vp4, 0.38 years (10). The clinical benefit is unsatisfactory either. Till now, there is no global consensus or standard guidelines for the treatment of HCC patients with PVTT, along with an urgency to find new treatments.

Recently, immunotherapy marks a new dawn in HCC management. IMbrave 150 study demonstrated an improvement in clinical benefit with atezolizumab (anti-PDL1 antibody) and bevacizumab (anti-VEGF antibody). According to IMbrave 150, 129 patients with macrovascular invasion included in the study had mOS of 14.2 months vs. 9.7 months (HR 0.68)) and mPFS of 6.7 months vs. 4.2 months (HR 0.59), which confirmed the effectiveness of ICIs combined with VEGF inhibitor in patients with PVTT. However, in 73 patients with Vp4 PVTT, the OS was 7.6 months, which is still unsatisfactory (11). In a prospective study by Lu et al., examined the efficacy of PD-1 inhibitors combined with Lenvatinib in HCC patients with major vascular invasion as conversion therapy. Successful conversion rate was 42.4%; median overall survival was 6.5 months (12).

Radiotherapy is increasingly used in advanced HCC and demonstrated encouraging clinical benefit in management of PVTT. Cheng et al. found that neoadjuvant radiotherapy reduced the extent of PVTT and improved post-operative survival rate reaching 75.2% at 12 month (13). In addition, radiotherapy upregulated PD-L1 in patients with HCC, potentiated the antitumor effect of immune checkpoint inhibitors and augmented cytotoxic T-cell infiltration in HCC tumors in immunocompetent mice (14).

Thus, we designed this study to evaluate the safety and efficacy of radiotherapy combined with lenvatinib plus PD-1 inhibitors as neo-adjuvant therapy in hepatocellular carcinoma with portal vein thrombus.

Methods and analysis

Study design

This is an open-label, single-arm, prospective, multi-center phase I trial in HCC patients with portal vein thrombus which will be conducted in 5 hospitals in China. (Figure 1). The study is being followed the Declaration of Helsinki and Good Clinical Practice. The protocol and its amendments have been approved by the ethics committee of Beijing Tsinghua Changgung Hospital (No. 21323-0-03). The recruitment started on

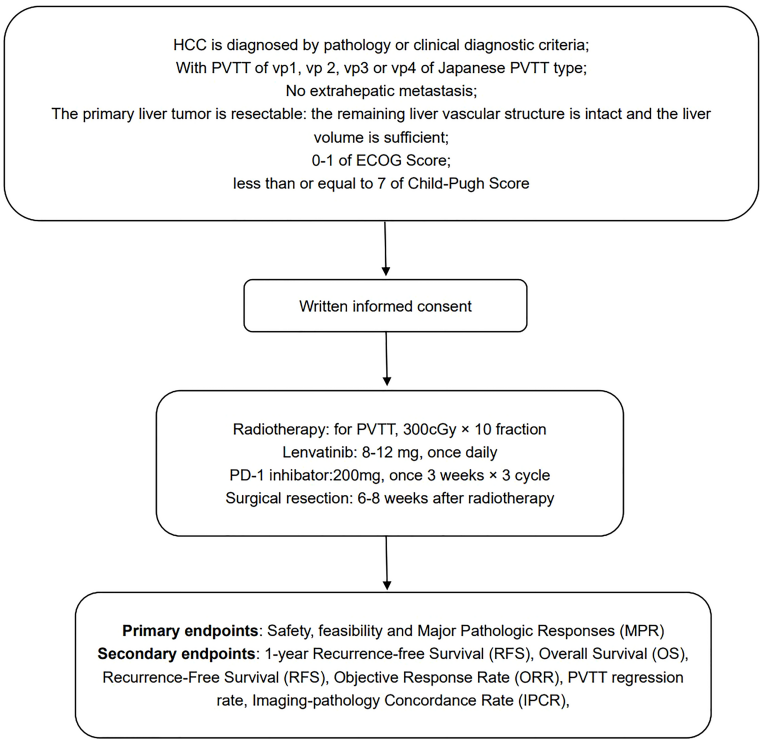

FIGURE 1
Study design.

December 01, 2022. The enrolment is estimated to complete in December 1, 2025.

Selection of subjects

Eligibility criteria

The patient inclusion and exclusion criteria are detailed in Table 1.

Interventional methods

Eligible patients will receive radiotherapy for PVTT and primary tumor. CT simulation localization will be performed before radiotherapy and the CT scan images will be transmitted to the treatment planning system in preparation for target delineation. The gross tumor volume will include liver tumor lesions and portal vein tumor thrombus displayed on the CT image. The clinical target volume margin will be 0.5cm for the liver tumor lesions and no expansion for portal vein tumor thrombus lesions. The interfractional margin will be set at 0.5cm and combined with internal motion compensation to form a field-specific planning treatment volume. RT dose is 30Gy (3Gy*10fractions). RT will be given from Monday to Friday, and will be finished in two weeks. Lenvatinib is started on the first day of radiotherapy (daily dose determined according to body weight, 8mg for bodyweight < 60 kg and 12 mg for bodyweight ≥ 60 kg) and will be discontinued 7 days before surgery.

The PD-1 inhibitor(sintilimab) is also started on the first day of radiotherapy, with a fixed dose of 200 mg every three weeks for three cycles. Surgery will be performed 6 to 8 weeks after radiotherapy (Figure 2). Dose adjustment, interruption, or discontinuation of lenvatinib and sintilimab according to the adverse events (AES) is detailed in Tables 2, 3.

Assessment

Tumor response assessment

Baseline CT/MRI scan will be performed within 28 days prior to the first treatment. The second CT/MRI scan will be done before surgery. Baseline and the second assessment must follow the same radiological procedures, which include chest CT and abdomen CT/MRI. RECIST v1.1 is utilized for assessment of treatment response.

Safety assessment

Routine blood tests, liver and kidney function tests will be performed once a week during the first two weeks. Laboratory

TABLE 1 Eligibility criteria.

	Inclusion criteria
1	Aged 18-70 years, no gender restrictions
2	Been diagnosed with HCC by histopathological or cytological examinations or meet the Chinese clinical diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" (2019 Edition)
3	Tumor thrombus in the main portal vein or branches (vp1, vp2, vp3 or vp4 of Japanese PVTT type) and without extrahepatic metastasis
4	The primary tumor is resectable: the remaining liver vascular structure is intact and the liver volume is sufficient, which is in line with the decision-making system for safe hepatectomy
5	ECOG performance status 0-1
6	Child-Pugh score ≤7
7	HBV DNA <500 IU/ml and have been receiving conventional antiviral therapy for HBV antigen-positive patients
8	For normal function of major organs, the following criteria should be met: 1. Adequate bone marrow function, defined as: Absolute neutrophil count (ANC ≥1.5 x 10^9 /L); Hemoglobin (Hb ≥8.5 g/dL) ; Platelet (PLT ≥ 75 x 10^9/L) 2. Adequate liver function, defined as: Albumin ≥ 2.8 g/dL, Bilirubin ≤3.0 mg/dL, Aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) were ≤ 5 times the upper limit of normal (ULN) 3. Adequate coagulation function, defined as: International Normalized Ratio (INR) of 2.3 or less 4. Adequate renal function, defined as: creatinine clearance > 40 mL/min, calculated according to the Cockcroft and Gault formula 5. Adequate pancreatic function, defined as: amylase and lipase ≤ 1.5 times ULN
9	Adequate blood pressure (BP) control with up to 3 antihypertensive drugs, defined as: BP ≤150/90 mmHg at screening, and there is no change for antihypertensive therapy within 1 week prior to Cycle 1/Day 1
10	The patient is expected to survive more than 3 months
11	No pregnancy or planned pregnancy
12	Witten informed consent
	Exclusion criteria
1	Extrahepatic metastasis
2	Diffuse liver cancer
3	Patients who have received targeted drugs and immune checkpoint inhibitors in the past
4	Hypersensitivity to lenvatinib or PD-1 inhibitor components
5	Patients with myocardial ischemia or myocardial infarction of grade II or above, and poorly controlled arrhythmias (including QTc interval ≥ 470 ms); according to the NYHA standard, grade III to IV cardiac insufficiency, or cardiac color Doppler ultrasonography indicates left ventricular ejection Blood fraction (LVEF) <50%
6	Abnormal coagulation function : INR>1.5 or prothrombin time (PT) > ULN + 4 seconds or activated partial thromboplastin time (APTT) >1.5 ULN, with bleeding tendency or receiving thrombolytic or anticoagulation therapy
7	Pregnant or breastfeeding women; patients with childbearing potential who are unwilling or unable to take effective contraceptive measures
8	Have a history of mental illness or abuse of psychotropic substances
9	Combined HIV-infected
10	History of liver resection, liver transplantation, interventional therapy, and other malignant tumors
11	Patients with active infection
12	With contraindications to radiotherapy
13	Patients with poor compliance such as floating population
14	Those who have participated in clinical trials of other experimental drugs or devices within four weeks
15	Those deemed unsuitable for inclusion by the investigator

tests such as blood routine, liver and kidney function, troponin-T, serum cortisol, and adrenocorticotropic hormone will be performed (once every three weeks for the rest before operation) to evaluate the safety of the treatment. The dosage will be adjusted according to the instructions if the patients have any safety issues.

Follow-up

Within one year after the operation, imaging evaluations will be performed every 3 months which including contrast-enhanced CT/MRI of the upper abdomen and plain CT of the chest. In the second year after surgery, imaging assessments will be performed every 6 months until subjects experience disease progression. After progression, survival follow-up will be performed every 6 months. Due to the small sample size of this study, if there will be a loss of follow-up in the following process, it is necessary to supplement the sample size to ensure 20 enrolled people. Clinical visit information is detailed in Table 4.

Sample size

The main study center treated 5 HCC patients with PVTT (all VP4) between 2020 and 2022. These patients underwent surgery after using the same neoadjuvant therapy as this trial. All patients achieved good efficacy, with a postoperative MPR of

Intervention	Week1	Week2	Week3	Week4	Week5	Week6	Week7	Week8	Week9
Lenvatinib	D1-7	D1-7	D1-7	D1-7	D1-7	D1-7	D1-7	D1-x*	
Sintilimab	D1			D1			D1		
Radiotherapy	D1-5	D1-5							
Surgery								Preoperative assessment	Surgery

*Stop 7 days before operation

Lenvatinib: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg. It will be used continuously until one week before surgery.

Sintilimab: It is administered as an intravenous infusion. The recommended dose is 200 mg once every 3 weeks until week 7.

Radiotherapy: Radiotherapy will be given only on weekdays during the first two weeks.

Surgery: After preoperative evaluation at week 8, eligible patients will undergo surgery.

FIGURE 2
Clinical trial process.

60% (3/5), and manageable safety profile, supporting this trial. Based on this result, we set the end-point of effective response rate as 60%. We simulated response rates of 10%, 20%, and 30% assumed as pathological effective naturatly before intervention. The recruiting time for whole population of the patients is 24 months, and the last enrolled patient will be followed for 12 months. Two-sided Tests with 80% power is used with type I error set at 0.05, and one-Sample tests for exponential hazard rate is used to calculate sample size. The sample size calculate by PASS software 2021 version is 6, 10 and 18 for an effective response rate 10%, 20% and 30%, respectively. Based on the maximum possible effective response rate as control at baseline, we finally set it as 30% and obtained a sample size of 18 that included 11 events. The final sample size is 20 patients, allowing for a 10% loss to follow-up.

Statistical analysis

This is an open-label, single-arm, phase I clinical trial and a planned 20 eligible subjects will be enrolled. Descriptive Analysis: The description of the quantitative indicator will give the median. Baseline Demographic Analysis: Descriptive analysis of baseline demographic data, and the chi-square test or survival analysis for numerical data in the experimental and control groups, depending on the data type. Analysis of evaluation indicators: Safety and feasibility, MPR rate, 1-year recurrence-free survival rate, ORR, PVTT regression rate, IPCR, ECOG score, tumor marker changes (AFP, PIVKA-II), ICG-R15 Changes, changes in liver function, etc. analysis of variance using two independent samples t-test, nonparametric test, repeated measures design according to data type. OS and RFS will use survival analysis according to data type. Safety evaluation: Adverse events will be described by the number and incidence, and detailed descriptions of the specific manifestations and degrees of all adverse events and their relationship with the drugs used. Since it is an exploratory study, the research data and results are subject to the investigator's evaluation, and a Data Monitoring Committee (DMC) is not specially established.

Outcome definitions

- Safety: the number of patients who reported incidence of grade ≥3 treatment-related adverse events (according to CTCAE v5.0);
- Feasibility: the number of patients who complete pre-op treatment and proceed to surgery;
- Major Pathological Response (MPR): a reduction in the proportion of surviving tumors below a clinically significant cutoff (≤10% of surviving tumors);
- 1-year recurrence-free survival: the proportion of all patients without HCC recurrence one year after liver resection;
- Objective Response Rate (ORR): the percentage of patients with complete response (CR) and partial response (PR) in all patients, and the response to treatment is based on the modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1);
- Imaging-Pathology Concordance Rate (IPCR): the proportion of all patients with consistent PVTT regression on preoperative imaging and postoperative pathological PVTT regression assessment;
- PVTT regression rate: the proportion of patients with PVTT regression after treatment, divided into PVTT regression rate assessed by imaging and PVTT regression rate assessed by pathology;

TABLE 2 Dose adjustment criteria of lenvatinib according to the AEs.

AEs	Degree of AEs	Management	Taper and resume lenvatinib mesylate
Hpertension	Grade 3 (despite optimal antihypertensive therapy)	Suspend	Remission to grade 0, 1 or 2.
	Grade 4	Permanently discontinue	Treatment must not be restarted
Pteinuria	≥ 2 g/24 hours	Suspend	Remission to less than 2g/24 hours
Nephrotic syndrome	—————	Permanently discontinue	Treatment must not be restarted
Renal insufficiency or kidney failure	Grade 3	Suspend	Remission to Grade 0-1 or Baseline
	Grade 4*	Permanently discontinue	Treatment must not be restarted
Heart dysfunction	Grade 3	Suspend	Remission to Grade 0-1 or baseline
	Grade 4	Permanently discontinue	Treatment must not be restarted
Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Any grade	Suspend	If remission reaches grade 0-1, consider restarting treatment at a reduced dose
Liver toxicity	Grade 3	Suspend	Remission to Grade 0-1 or baseline
	Grade 4*	Permanently discontinue	Treatment must not be restarted
Arterial thromboembolism	Any grade	Permanently discontinue	Treatment must not be restarted
Bleeding	Grade 3	Suspend	Remission to Grade 0-1
	Grade 4	Permanently discontinue	Treatment must not be restarted
Gastrointestinal perforation or gastrointestinal fistula	Grade 3	Suspend	Remission to Grade 0-1 or baseline
	Grade 4	Permanently discontinue	Treatment must not be restarted
Parenteral fistula	Grade 4	Permanently discontinue	Treatment must not be restarted
QT interval prolongation	>500 ms	Suspend	Remission to ≤ 480 ms or baseline
diarrhea	Grade 3	Suspend	Remission to Grade 0-1 or baseline
	Grade 4 (although medically managed)	Permanently discontinue	Treatment must not be restarted

* It can be treated according to Grade 3 adverse reactions if it is judged to be non-life-threatening when the adverse reaction is laboratory abnormal Grade 4.

- Median overall survival (mOS): the median difference (in months) between the date of study enrollment and the date of death due to any cause. Patients still alive at the end of the study will also be treated as censored, with the last known survival date as the last survival time;
- Recurrence-free survival (RFS): from radical resection to the date of the first documented tumor into recurrence or death from any cause, whichever occurred first.

Anticipated results

Safety and feasibility will be used as a primary endpoint, and MPR, one-year recurrence-free survival, ORR, IPCR, PVTT regression rate, OS and RFS will be as secondary endpoints. We expect to observe the safety data and the surgical conversion rate of the study group in order to assess the feasibility of subsequent phase II clinical study. And we will use these outcomes to determine the sample size of the further clinical study.

Discussion

Portal vein tumor thrombus (PVTT) is a common phenomenon in hepatocellular carcinoma (HCC) patients, classified by the VP classification of Japan (15) or Cheng's type of China in clinical practice. VP classification appeared earlier and was more widely used worldwide so in this study VP classification will be used as the classification standard of PVTT.

TABLE 3 Adjustment criteria of PD-1 inhibitor according to the AEs.

AEs	Degree of AEs	Management	Taper and resume lenvatinib mesylate
Pneumonia	Grade 2	Suspend	Remission to grade 0-1.
	Grade 3 or 4 or recurrent grade 2	Permanently discontinue	Treatment must not be restarted
Nephritis	Grade 2, creatinine greater than 1.5 times and less than 3 times of ULN	Suspend	Remission to grade 0-1.
	Grade 3 or 4, creatinine greater than 3 times of ULN	Permanently discontinue	Treatment must not be restarted
Colitis	Grade 2 or 3	Suspend	Remission to grade 0-1.
	Grade 4 or recurrent grade 3	Permanently discontinue	Treatment must not be restarted
Endocrine disease	Adrenal insufficiency Symptomatic hypophysitis Type 1 diabetes with hyperglycemia ≥ grade 3 (fasting blood glucose > 250 mg/ml or 13.9 mmol/L) or related ketoacidosis Hyperthyroidism ≥ grade 3	Suspend	Remission to Grade 0-1. For patients with grade 3 or 4 endocrine disease who have improved to grade 2 or lower, and who have clinical symptoms that can be controlled by hormone replacement, consider continuing PD-1 inhibitors after reducing the dose of corticosteroids, otherwise treatment should be discontinued. Hypothyroidism can be managed with replacement therapy without interruption of treatment.
Hepatitis	Grade 2, ALT or AST > 3-5 times ULN or TBIL > 1.5-3 times ULN	Suspend	Remission to Grade 0-1.
	Grade 3-4, ALT or AST > 5 times ULN or TBIL > 3 times ULN	Permanently discontinue	Treatment must not be restarted
Skin reaction	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Suspend	Remission to Grade 0-1.
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Treatment must not be restarted
Other immune-related adverse reactions	Depending on the severity and type of reaction, grade 2 or 3	Suspend	Remission to Grade 0-1 or baseline
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome	Permanently discontinue	Treatment must not be restarted
	Grade 4 or recurrent grade 3	Permanently discontinue	Treatment must not be restarted
Infusion-related reactions	Grade 3 or 4	Permanently discontinue	Treatment must not be restarted

Our protocol explores the safety and efficacy of radiotherapy combined with lenvatinib and PD-1 inhibitor (sintilimab) as neoadjuvant therapy for hepatocellular carcinoma complicated with PVTT, which has good prospects.

First, radiotherapy is an effective treatment modality for PVTT. A previous report pointed out that the response rate of radiotherapy in patients with different PVTT classifications was 32.6%-100%, and the 5-year survival rate and the median OS were 5.1%-58.0% and 5.3 to 27.0 months, respectively (16). Low-dose radiotherapy can enhance immunity, which provides a curative effect in PVTT than liver tumors. A Japanese study performed 30-60Gy/10-12F radiotherapy on the tumor thrombus of the main portal vein and its branches, and then surgical resection was performed within 2 weeks after radiotherapy. The results showed that the postoperative PCR rate reached 53%. Another controlled study in China found that neoadjuvant radiotherapy improved PFS and OS in PVTT patients, with the radiation dose of only 3Gy*6F. Low-dose radiotherapy reducing radiation damage to normal tissues and organs can effectively reduce the incidence of adverse reactions, improving the quality of life. In this study, the radiotherapy dose was determined to be 3Gy*10F.

Second, combined targeted and immune therapy is an effective treatment for HCC, having a synergistic effect with radiotherapy. The improvement of the objective response rate of systemic therapy drugs, such as various anti-angiogenic drugs and immune checkpoint inhibitors (ICIs), has brought more possibilities for preoperative treatment. Moreover, low-dose radiation converts TAM to M1 phenotype, infiltrating existing T cells into tumors, thereby promoting the transformation of tumors from “cold” to “hot” (17, 18). In addition to that, some clinical studies suggested that the combination of radiotherapy and immunization may benefit the survival of patients with unresectable HCC (19, 20).

TABLE 4 Clinical visit information diagram.

	Screening period	Neoadjuvant Therapy(RT+ Sintilimab +Lenvatinib)			Operation			All eligible patients(Non-operated patients will be counted from the day of neoadjuvant failure and surgical patients will be counted from the first postoperative day)		
		Neoadjuvant therapy week 2 (during radiotherapy)	Neoadjuvant therapy week 4(before the start of cycle 2 of sintilimab)	Neoadjuvant therapy week 7(before the start of cycle 3 of sintilimab)	Before Operation	During Operation	1 month ± 10 days after operation	3 month ± 10 days	1st year every 3 months ±10 days	From 2nd year, every 6 months ± 10 days until disease progression or death
Demographics	√									
Past medical history	√									
Vp typing of PVTT	√							√		
Child-Pugh score	√			√	√		√			
ECOG score	√			√	√		√	√	√	√
ICGR-15	√				√					
Routine blood test	√	√	√	√	√		√	√	√	√
Liver and kidney function test	√	√	√	√	√		√	√	√	√
Thyroid function test	√			√						
ACTH test (8:00 am.)	√			√						
Serum cortisol test (8:00 am.)	√			√						
Troponin	√		√	√						
AFP、PIVKA-II	√				√		√	√	√	√
immune-related biomarkers(PD-L1、TMB)							√			
Immune cell typing (CD4+ T cells, CD8+ T cells)	√				√		√			

(Continued)

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TABLE 4 Continued

	Screening period	Neoadjuvant Therapy(RT+ Sintilimab +Lenvatinib)			Operation			All eligible patients(Non-operated patients will be counted from the day of neoadjuvant failure and surgical patients will be counted from the first postoperative day)		
		Neoadjuvant therapy week 2 (during radiotherapy)	Neoadjuvant therapy week 4(before the start of cycle 2 of sintilimab)	Neoadjuvant therapy week 7(before the start of cycle 3 of sintilimab)	Before Operation	During Operation	1 month ± 10 days after operation	3 month ± 10 days	1st year every 3 months ±10 days	From 2nd year, every 6 months ± 10 days until disease progression or death
Abdominal image	√				√		√	√	√	√
Lung imaging	√				√			√	√	√
ECG	√				√					
Inclusion and exclusion criteria judgment	√									
Neoadjuvant therapy		√	√	√						
Operation						√				
Efficacy evaluation				√				√	√	√
Adverse event		√	√	√	√	√	√	√	√	√
Concomitant medication/ therapy		√	√	√			√	√	√	√

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Third, a few studies recently have explored neoadjuvant therapy of HCC. The final results of nivolumab alone or in combination with ipilimumab in the perioperative period of resectable HCC, a phase II randomized controlled, open-label study, were reported at the 2020 ASCO meeting. The results demonstrated that among 27 evaluable patients, the pCR rate was 19%, with 21 patients undergoing planned surgery (21). Another study in mildly resectable or locally advanced HCC reported at ASCO-GI 2021 showed that neoadjuvant therapy of cabozantinib combined with nivolumab achieved margin-negative resection in 12 of 15 patients, of which 5 were major/complete pathological response (22).

To date, there are no study on neoadjuvant therapy using lenvatinib and PD-1 inhibitor combined with radiotherapy for BCLC stage C. This study will provide preliminary evidence for the safety and efficacy of radiotherapy combined with lenvatinib plus PD-1 inhibitors (sintilimab) as neoadjuvant therapy for resectable HCC with PVTT. In addition, some interesting questions, such as the PVTT regression rate with neoadjuvant therapy and the consistency of imaging and pathological assessment of PVTT regression rates, will be explored in this study. In summary, this study may supplement the clinical decision-making evidence in the neoadjuvant treatment of BCLC stage C patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by ethics committee of Beijing Tsinghua Changgung Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JD was the principle investigator of the study who supervises and coordinates the whole project. SY and GoL as principle investigators were involved in the study conception and design. GuL, BS, ZZ, HY, CZ, YX, YY will be involved in the acquisition of data. GoL and GuL will be involved in neo-adjuvant therapy. SY and BS will be involved in surgery. ZZ and CZ will be involved in imaging assessment. HY and YX will be involved in pathological evaluation. YY and ZY will be responsible for follow-up of the enrolled patients. GuL and BS will be involved in the analysis and interpretation of data. GuL were involved in draft in the manuscript. XZ will be in charge of data statistics. GuL and BS were involved in revising the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Narimantas Samalavicius,
Vilnius University, Lithuania
Chris Varghese,
The University of Auckland,
New Zealand

*CORRESPONDENCE
Birgitte Schantz Laursen
bisl@rn.dk

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Coping strategies and considerations regarding low anterior resection syndrome and quality of life among patients with rectal cancer; a qualitative interview study

Birgitte Schantz Laursen[1,2*], Gitte Kjær Sørensen[3], Margit Majgaard[3], Line Byskov Jensen[3], Karen Irene Jacobsen[1], Dorte Kløve Kjær[1], Therese Juul[3], Peter Christensen[3] and Anette Højer Mikkelsen[1]

[1]Sexology Centre and Gastrointestinal Surgical Outpatient Clinic, Aalborg University Hospital, Aalborg, Denmark, [2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, [3]Department of Surgery, Aarhus University Hospital, Aarhus, Denmark

Introduction: Low anterior resection syndrome (LARS) is defined as disordered bowel function following rectal resection, which is detrimental to quality of life (QoL). A recent international consensus definition of LARS stresses the importance of focusing on both the symptoms and the consequences that the symptoms have for the individual patient as studies indicate that LARS has a negative impact on patients' QoL. However, an ongoing PROM study investigating late sequelae after rectal cancer finds that a minor proportion of patients scoring major LARS experience none or only little impact on quality of life

Aim: The aim of this study was to identify patients' considerations and coping strategies to establish why the burden caused by major LARS had little or no influence on their QoL.

Materials and methods: This was a qualitative interview study based on 21 semi-structured individual telephone interviews with patients treated for rectal cancer. Data were analysed using a hermeneutic inspired thematic analysis.

Results and conclusion: Three themes emerged from the analysis; Adapting new life situation, Altering life perception and the Importance of relationships. Major LARS and its consequences following rectal cancer may be managed or altered by adopting problem-focused and emotion-focused coping strategies. Maintaining a positive attitude and having a good network of family and friends constitute a surplus, allowing patients to cope with the need for changed behaviour and appreciate the life that they have been given. Accepting that

major LARS and its consequences cause limitations in life allowed patients to change their normality threshold over time.

KEYWORDS

low anterior resection syndrome, major LARS, quality of life, coping strategies, qualitative study, qualitative interviews, thematic analysis

1 Introduction

The prevalence of cancer in the Northwest European adult population is estimated at 4.4%, and the overall survival rate of cancer patients has increased in recent decades owing to improved treatment modalities (1). Every year, 45,000 Danes are diagnosed with cancer, and there are about 365,000 survivors of cancer treatment in Denmark (2). One logical consequence of the increased survival rate is a shift in focus from biomedical therapeutic procedures to improving survivorship skills and quality of life (QoL). Attention to late sequelae after cancer has, therefore, risen.

Worldwide, colorectal cancer is one of the most predominant cancers, representing 10.9% of all cancers in males and 9.5% in females (3). A common late sequela following a low anterior resection (LAR) for rectal cancer is the LAR syndrome (LARS), which is pragmatically defined as disordered bowel function after LAR leading to a deterioration of QoL (4). A recent international consensus definition of LARS stresses that it is of great importance to focus both on the symptoms and the consequences that the symptoms have for the individual patient (5). Studies have indicated that LARS has a negative impact on patients' QoL in up to 80% of cases with major alterations in 40%. Still, a recent study found that from a clinical viewpoint, the burden caused by LARS on the QoL of patients treated for low and mid rectal cancer is frequently underestimated (6). However, an ongoing patient-reported outcome measures (PROM) study investigating late sequelae after rectal cancer found that some patients scored none or only little impact of major LARS on their QoL. The inconsistent correlations between symptoms measured by the LARS score and QoL could be caused by limitations of the LARS score, and it would therefore be of interest to see how patient's perspectives and coping strategies interact with their LARS to impact on their QoL. Understanding the mechanism behind and getting insight into the perspectives and the coping strategies used by patients who experience no or little impact on their QoL despite major bowel dysfunction may be used by healthcare professionals to support and guide patients who have major LARS but experience great impact on their QoL.

Thus, the aim of this qualitative study was to identify patients' considerations and coping strategies explaining why the burden of major LARS had potentially little or none influence on their QoL.

2 Methods

The study design was qualitative, and the study was conducted under the Danish Cancer Society Centre for Research on Survivorship and Late Adverse Effects after Cancer in the Pelvic Organs (7). The study was based on 21 individual semi-structured telephone interviews with patients undergoing LAR for rectal cancer and experiencing LARS symptoms. The applied interpretive data-driven thematic analysis gives voice to patients, which is useful when focusing on patient experiences (8). The study was reported following the Consolidated Criteria for Reporting of Qualitative Research (COREQ) (9).

2.1 Participants

The participants were recruited from the study "Systematic screening for late sequelae after colorectal cancer" initiated by the Danish Cancer Society Centre for Research on Survivorship and Late Adverse Effects after Cancer in the Pelvic Organs. In the study, patients with colorectal cancer (CRC) complete questionnaires at 3, 12, 24 and 36 months after surgery. The selected domains in the questionnaire include bowel, urinary and sexual dysfunction, chronic pain and stoma problems (10). The participants included in the present study had a LAR for rectal cancer with or without chemo-/radiotherapy, and they had no stoma at the time of the interview. Participants who previously had a temporary diverting stoma had it reversed a minimum of six months prior to the interview. All participants had completed the PROMs and scored major LARS, but at the same time they stated that their bowel function had no or only little impact on their QoL. The patients were invited to participate in the present study consecutively between one and three years after surgery. A total of 21 patients were included in the study to ensure data saturation (11).

2.1.1 Inclusion criteria

The sampling was purposeful and criterion based.

1. Rectal cancer patients undergoing a LAR, without a present stoma, included in the study "Systematic screening for late sequelae after colorectal cancer",
2. Patients who scored major LARS and experienced no or only little impact of bowel function on QoL.

Participant characteristics are presented in Table 1.

2.2 Data collection

The telephone interviews were conducted by authors 2-5 who all are registered nurses, based on a semi-structured interview guide, Table 2, with open questions in line with the aim of the project and research in the field (9). As an introduction, the participants were asked to present themselves and their experiences during their disease course and treatment. The interview focused on the patients'perspectives, experiences and thoughts in relation to their bowel dysfunction and its impact on their QoL (Table 2).

TABLE 1 Patient characteristics.

Patient id	Age	SexM/F	LARS Score	Impact on Quality of life*	Work situation	Civil status	Previous stoma	Month since operation
1	74	M	37	a little	retired	married	yes	12
2	54	M	34	a little	working	married	yes	12
3	72	M	31	a little	retired	married	no	12
4	66	F	33	a little	retired	married	yes	12
5	72	M	33	a little	retired	married	yes	12
6	65	M	37	a little	retired	married	no	3
7	62	F	36	a little	working	married	yes	24
8	70	F	37	a little	retired	married	no	3
9	63	M	36	a little	working	married	no	24
10	84	F	37	not at all	retired	married	yes	12
11	59	M	39	a little	retired	single	no	12
12	63	F	36	a little	working	married	no	24
13	60	M	35	a little	working	married	yes	12
14	50	F	36	a little	working	married	yes	12
15	68	M	35	a little	retired	married	yes	12
16	60	F	37	a little	working	married	yes	12
17	54	F	37	a little	working	married	yes	12
18	73	F	31	a little	retired	widow	yes	12
19	73	F	39	a little	retired	married	yes	12
20	75	M	34	a little	retired	married	yes	12
21	50	F	36	a little	working	married	yes	12

*Question: overall, how much does your bowel function affect your quality og life? Options for answering not at all, a little, some, a lot.

TABLE 2 Interview guide.

Research question	Interview theme
How patients manage their LARS symptoms in everyday life. Despite LARS, why is their QoL not affected?	**We can see from your answer to the questionnaire that your stool pattern has changed, what does a normal day look like for you?**
	How do you adjust to your bowel dysfunction? (Has anything in the house decor, diets, etc., changed)?
	How does your bowel dysfunction affect your day and your thoughts?
Why do the patients' LARS symptoms NOT affect his/her QoL and life development?	**Have you stopped doing things because of your bowel dysfunction that you did in the past? (holidays, cinema visits, restaurant visits, visiting friends and family, walking, shopping, etc.)?**
	What makes you think you have a good life?

The individual interviews allowed participants to raise topics and express thoughts that they considered important. The interviews were audiotaped and lasted 15-30 minutes. Data were collected from October 2020 to June 2021 and all interviews were transcribed.

2.3 Data analysis

Data were analysed collaboratively by the authors. To search for meaningful patterns (themes) across the interviews, an inductive, data-driven thematic analysis was conducted (8). The interpretation of the interviews was initiated by transcription of the verbal data, obtaining an overview of all the interviews focusing on the patients' perspectives, experiences and thoughts. Then, more structured and analytically meaningful themes and patterns were identified, defined and named. In the final phase, the themes were interpreted and discussed in relation to other research and theories in the explored field.

2.4 Ethical considerations

Ethical considerations followed the directions of the Helsinki Declaration. All participants were informed, and confidentiality was ensured. Recommended procedures to ensure informed consent and voluntariness were followed (7). The study was reported to and approved by the Danish Data Protection Agency (no. 2019-110). Data were anonymized using numbers and was stored securely.

3 Results

Three themes emerged from the narratives shared by the patients on their experiences living and coping with LARS following rectal cancer. The themes were: Adapting to a new life situation; Altering life perception and Importance of relationships.

3.1 Adapting to a new life situation

All the patients had changed various aspects of their everyday life to cope with the changes introduced due to bowel dysfunction. They had become more observant of how their body and their bowel movements reacted to diet, activities and medication, which had allowed them to plan their lives so that the disease affected them as little as possible. In general, patients had accepted and learned to live with their bowel problems: "I have learned to adapt". (13)

One of the men explained how increased attention to his body's signals helped him to control his defecation:

"Well, I actually think that I have become a bit better, you know, at sensing when I need to go … and, usually, I can feel that I have finished … but occasionally I feel nothing and that's when things get messy (involuntary bowel movements)". (17)

One of the women had trained her pelvic floor, allowing her to better control her bowel movements:

"Well, I attended rehabilitation and learned how to train my pelvis … I think that helps me keep my bowels back for longer… (19)

Another man described how he dealt with his increased flatus:

"I'm not bothered by it, I just sit there, real quiet, and lean to one side for a moment to let out a bit of gas. Usually, It's silent or the sound is so low that it doesn't matter, even though you are with other people". (20)

Most patients described how, over time, they had become aware of how their diet and fluids affected their bowel function. Based on their observations, they had adopted individual strategies so that their daily lives were less affected by their bowel dysfunction. These strategies comprised the ingredients in the food and the quantity of food ingested.

"I used to just dig in when I was enjoying a meal in good company, I just kept eating, I don't do that anymore because when I do I feel like shit the next day". (9)

Not all patients refrained from having their favorite dishes. They arranged themselves and in cases in which they knew from experience that a certain type of food would affect their bowel movements, they made sure that they were close to a toilet.

"It's because I know how to tackle it, right. I think that I know how to handle it really well. I shouldn't start out by having beans or cabbage or something like that if I know that I'll be going out later in the evening (laughs), because then you never know what might happen. Let's say that we decide to have a nice lunch with some schnapps and beer, then we'll do so at home where I can get to the toilet without delay". (1)

If the patients knew that they might not have access to a toilet, some of them chose to use a diaper as security.

"Let's say that I'm going out and that I'm unsure if there's a toilet close by. Well, then I'll just put on a diaper. And that will allow me to feel safe". (1)

Other patients regulated their bowel movements by adjusting their food and drink intake.

"I need to plan ahead if I'm going travelling … ehh … then I'll fast until I reach my destination, mostly because then I don't need to make sure that a toilet is close by". (7)

In addition to considering the amount of food and when to consume it, patients had also figured out which foods to avoid not to experience intestinal problems.

"I've learned things like avoiding spicy food. Basically, food shouldn't be too spicy or fatty and onion will

also get you into trouble. All of the things that typically get your intestines going, I'm more sensitive to those now." (13)

Patients occasionally used medication to control their bowel function; medication that stopped or promoted bowel movements. A single patient utilized the side effects of morphine to gain a night's rest:

"And I take 5 or 10 milligrams of morphine every night to get a good night's sleep. I don't take it to manage pain, it's to calm my peristalsis". (9)

A patient explained that when he could feel that he needed to go to the toilet 3-4 times within a short period of time, he took medication to slow down his bowel function:

"Once in a while, I don't get to the toilet in time and then things get messy; sometimes I have to take off towards the toilet up to four times … then I take one of the stop pills that I got at the hospital; otherwise I can't handle it". (17)

One of the interviewed males experienced that bowel dysfunction prevented him from activities that he could before, and this had added to his QoL:

"I'm a bit of a nature freak … I find that to be quality of life. I used to go hunting a lot and hiking and sleeping in shelters and stuff like that. You just don't do that anymore". (2)

3.2 Altering life perception

A person's basic perception or attitude towards life is typically reflected in his or her behaviour and thoughts. In the present study, the patients' life attitude played a considerable role in determining how they dealt with their bowel problems and the ensuing changes. They had accepted their new living conditions, had chosen to adopt a positive outlook on life and were thankful that they were alive. In that context, the bowel problems were not allowed to take over.

One of the men had put it as follows:

"But then, I say, you know what, if my gut problems are what allows me to stay alive then I can live with it. Sure, it can be annoying and some days are worse than others, but I take that in my stride". (3)

Another patient strategy was to compare themselves with others and find that they felt significantly better than some of the patients they met at the hospital or in the surrounding community or that their situation was far better than theirs.

For some of the patients, it was important that people surrounding them could not see that they were ill; this meant that they were not constantly reminded that they had been ill and now had bowel dysfunction. One of the patients expressed this as follows:

"You know what, nobody can see that I'm ill, and that is a good thing because no one is looking at me and talking about me. There's a young girl in town, 19 years old, I think. She has lost a foot to cancer and everybody can see that". (14)

In addition, most patients had a stoma immediately after their surgery and nearly all patients found that their current intestinal problems were preferable to the problems they had experienced with the stoma:

"I'm glad I got rid of the stoma. That was no fun at all, definitely not. I couldn't keep any food in me. It all passed right through, and I lost a lot of fluids if I ate stuff I weren't supposed to … I figured out that bananas and spicy buns worked. Things went better If I only had those. Now, I think, I'm nearly normal" (4)

The same patient compared her current situation to her stoma period, noting:

"If I had still had the stoma, I would have had problems, or it would have affected my quality of life more ". (4)

Not neglecting or repressing the problems you encounter in life and being open to family and friends and involving them in the problems helped patients cope the challenges that their gut problems presented them with.

One patient explained that letting his surroundings know how he feels made him feel better:

"That everyone sort of knows how I feel, it's important for me to be open about it and, like, just talk about it, so that people around me don't feel uncomfortable and that they might say something inappropriate". (17)

Having an open approach to the problems you experience in life and being open to the people surrounding you so that they know how you feel helped patients deal with the challenges that their bowel problems presented.

How one's psyche is and how one generally tackles life's challenges is also evident in situations where one has to learn to live with the late effects of chronic illness.

A man explained:

"Generally, I think I'm a tolerant guy. I get used to lots of stuff, right? That's just the way it is. But I have, as I said before, I have chosen that this would not bother me. It would not control my life, so I just try to make things work". (2)

Another man noted:

"But I think, I can't do anything about it anyway. So why the heck should I feel sad and angry and blue about it". (3)

3.3 Importance of relationships

Having a good network was very important when you are affected by an illness and have to live with late effects that affect your life. Experiencing support from family and friends meant for many that the illnesses became easier to deal with.

"Well, I can only say that I have a lovely life as a senior citizen, I enjoy spending time with my wife and we have fun together. That's quality of life. We have many friends and they visit us and we visit them. I don't let it [the late effects] affect my life". (20)

Another woman added:

"It's important to be enjoying your marriage and that you have a strong relationship with your children and grandchildren, I'd say. That would be it". (10)

A good close and intimate relation was very important for most of the patients:

"Well, I have a loving husband and all, and we're enjoying life and have sex. So things are working out fine". (8)

Not only partners were important; so were supportive good friends:

"And I enjoy going to the beach, along the waterfront, just taking it all in. Sometimes I bring a friend. Then we go for a long walk and talk about important things in our lives". (8)

4 Discussion

To our knowledge, this is the first study identifying coping strategies and considerations that facilitate living a nearly normal life despite cancer experience, symptoms and their long-term consequences for daily life. The themes identified in this study were: adapting to a new life situation; altering life perception; and the significance of relationships. These three coping strategies, some of which were developed during the patients' cancer experience, helped them integrate their cancer experience into their everyday lives and face the physical and psychosocial challenges arising from cancer, and allowed them to live their lives as normally as possible.

The ability to find meaning and coherence in life is related to the ability to cope with the stressors to which we are exposed. According to the Israeli sociologist Antonovsky's qualitative concept "sense of coherence", finding meaning in life is associated with feelings of comprehensibility, manageability and meaningfulness. To achieve a strong sense of coherence presupposes that the person experiences predictability, stress balance and a measure of influence on his or her life situation (12). In the present study, bowel dysfunction may be defined as a stressor. To achieve a strong sense of coherence, it is of essential importance that the patients are able to cope with the external symptoms and their changed life situations. However, humans' ability to deal with stressful challenges is closely linked to their life attitudes and ability to apply coping strategies.

According to Lazarus and Folkman, humans have two basic coping strategies, problem-focused and emotion-focused coping, as responses aimed at "managing or altering the problem causing distress" and "regulating emotional responses to the problem," respectively (13). The former focus on solving or processing problems, expanding action options, seeking information or confrontation. In contrast, the latter focus on regulating emotions and discomfort and mentally shifting focus or seeking comfort/relief. (Ibid).

The patients in this study applied both problem- and emotion-focused coping. They adopted a problem-focused strategy by which they actively aimed to address the challenges that their LARS symptoms presented them with. Several of the patients had exercised an awareness of their body and had been able to sense the signals from the intestinal system so that they could be eliminated in situations of willing bowel movements, and one says that she exercised the pelvic floor to improve control over her bowel movements. Another problem-focused strategy was to adjust the diet to limit bowel problems. A single patient found that if he took morphine, which reduces intestinal peristalsis, he could avoid having to run to the toilet. Some patients accepted that the bowel dysfunction had introduced limitations into their lives and had thus changed their normality threshold over time. This is in line with findings in a study by Bohlok et al. who found no correlation between overall QoL and LARS and argued that this might be due to the patient's ability to accept and adjust to their new life situation (6). More than half of the patients in the present study were retired, which also made it easier for them to plan their day according to their bowel dysfunction.

In relation to the emotion-focused strategy, patients focused on understanding the emotions and discomfort associated with LARS by shifting their focus and using their network. One strategy used to shift the focus was to compare their own current situation with a previous situation that they felt was much more serious. Half of the patients initially had a temporary stoma which was subsequently reversed, and some of them experienced that the time with the stoma involved far more challenges and discomfort, which had a positive impact on their perception of life with LARS.

Other patients compared their current situation to that of others, thereby putting their experiences into perspective and reaching the conclusion that they were much better off than some others. One of the patients compared his own situation with that of a 19-year-old girl who has had her leg amputated due to cancer and concluded that her situation was "far worse". Scaling your own experience and measuring your suffering against that of others is coined "response shift" and has also been observed as a coping strategy in other studies (14, 15)

Having a good family and a strong network helped patients cope with the situation. Studies have shown that partners constitute a particularly important emotional support, which is directly associated with a higher mental and physical health related QoL (16). Haviland et al. concluded that poorer social support is significantly associated with a poorer health related QoL in colorectal cancer (17). Similarly, a recent questionnaire survey among Danish cancer survivors found that support from a relative was the most important factor in overcoming a cancer course (18).

Family and friends can provide support by being present and by listening to the patient, but they may also help divert

attention from cancer and shift the patient's focus to things in life that are of great importance. Suffering decreases when friends and family members take an active part in the disease course, not only during the acute phase but also in the subsequent period. This is supported by a study (19) arguing that suffering must be understood in a social context. If the surroundings do not understand the importance of the patient's suffering, the patient must bear the suffering alone, which may aggravate the process by adding a feeling of loneliness (19). Studies show that loneliness may lead to greater depressive symptoms and poorer QoL than in patients who experience no loneliness (20, 21).

Experiencing joy of life gives courage to live and promotes the unfolding of life, helping the patients to feel less inhibited and limited by their bowel dysfunction and the ensuing consequences. People who adopt a positive attitude, feel more joy and can achieve a strong sense of coherence and self-care ability (22).

Limitations of the study is according to data saturation as it is not possible to achieve a 100% data saturation. Furthermore, the homogeneity of the sample with regard to ethical and geographical representation may limit the generalizability or findings to more diverse population. Moreover patients' considerations and coping strategies might be reducing the negative impact on QoL in major LARS, but it could also be at play in minor LARS therefore the causal relationship requires further study, as treatments, medication etc. also can explain reduced impact on QoL.

5 Conclusion

Bowel dysfunction and its consequences after rectal cancer may be managed or improved by using both problem-focused and emotion-focused coping strategies. Being able to alter life perception and having a good network of family and friends produces a surplus allowing patients to adapt to the need for changed behaviour and to appreciate the life that they have been given. Accepting that bowel dysfunction and its consequences come with limitations in life has allowed the patients to change their normality threshold over time.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: BL, GS, MM, LJ, KJ, DK, TJ, PC, and AM. Methodology: BL and AM. Data collection: GS, MM, LJ, KJ, and DK. Data analysis: BL, GS, MM, LJ, KJ, DK, and AM. Preparation of the original draft: BL. Writing, review, and editing: BL, GS, MM, LJ, KJ, DK, TJ, PC, and AM. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Liu Yiqiang,
Beijing Cancer Hospital, China
Xin-Lin Chen,
Guangzhou University of Chinese Medicine, China

*CORRESPONDENCE
Salvador Morales-Conde
smoralesc@gmail.com
Zuli Yang
yangzuli@mail.sysu.edu.cn

†These authors have contributed equally to this work

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A retrospective analysis based on multiple machine learning models to predict lymph node metastasis in early gastric cancer

Tao Yang[1,2†], Javier Martinez-Useros[3,4†], JingWen Liu[5†], Isaias Alarcón[2†], Chao Li[6], WeiYao Li[1,3], Yuanxun Xiao[1], Xiang Ji[1], YanDong Zhao[7], Lei Wang[5], Salvador Morales-Conde[2*] and Zuli Yang[1*]

[1]Department of Gastrointestinal Surgery, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, Guangdong Institute of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University Guangzhou, Guangdong, China, [2]Unit of Innovation in Minimally Invasive Surgery, Department of General and Digestive Surgery, University Hospital "Virgen del Rocio", Sevilla, Spain, [3]Translational Oncology Division, OncoHealth Institute, Health Research Institute - Fundacion Jimenez Diaz, Madrid, Spain, [4]Area of Physiology, Department of Basic Health Sciences, Faculty of Health Sciences, Rey Juan Carlos University, Madrid, Spain, [5]Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong, China, [6]Faculty of Medicine, Autonomous University of Madrid, Madrid, Spain, [7]Department of Pathology, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Background: Endoscopic submucosal dissection has become the primary option of treatment for early gastric cancer. However, lymph node metastasis may lead to poor prognosis. We analyzed factors related to lymph node metastasis in EGC patients, and we developed a construction prediction model with machine learning using data from a retrospective series.

Methods: Two independent cohorts' series were evaluated including 305 patients with EGC from China as cohort I and 35 patients from Spain as cohort II. Five classifiers obtained from machine learning were selected to establish a robust prediction model for lymph node metastasis in EGC.

Results: The clinical variables such as invasion depth, histologic type, ulceration, tumor location, tumor size, Lauren classification, and age were selected to establish the five prediction models: linear support vector classifier (Linear SVC), logistic regression model, extreme gradient boosting model (XGBoost), light gradient boosting machine model (LightGBM), and Gaussian process classification model. Interestingly, all prediction models of cohort I showed accuracy between 70 and 81%. Furthermore, the prediction models of the cohort II exhibited accuracy between 48 and 82%. The areas under curve (AUC) of the five models between cohort I and cohort II were between 0.736 and 0.830.

Conclusions: Our results support that the machine learning method could be used to predict lymph node metastasis in early gastric cancer and perhaps provide another evaluation method to choose the suited treatment for patients.

KEYWORDS

early gastric cancer, endoscopic resection, gastrectomy, lymph node metastasis, artificial intelligence, machine learning

Introduction

Gastric cancer is one of the most common and deadly cancers in the world (1). According to GLOBOCAN 2021 data, gastric cancer is the third leading cause of cancer deaths worldwide, following only lung and liver cancers in overall mortality (2). Fortunately, because of the improvement in diagnosis and treatment, the survival rate for gastric cancer has been improved in recent years (1, 3, 4). Based on a report from the global surveillance of trends in cancer survival programs, age-standardized 5-year net survival for stomach cancer was below 30% in most countries, but high in Korea (69%) and Japan (60%), where it increased by up to 10% between 2000–2004 and 2010–2014; this is likely to be associated with endoscopic screening programs for early detection (5). Therefore, it is crucial to identify gastric cancer patients in the early stage.

Early gastric cancer (EGC) is defined as a stomach lesion confined to the mucosa and/or submucosa, regardless of its area or lymph node metastatic (LNM) status (6). Due to advances in endoscopic therapeutic techniques, the EGC has usually been diagnosed in the early detection and treated by endoscopic submucosal dissection (ESD) (7, 8). Many studies have shown that EGC has a 5-year survival rate of near 90% (9, 10). As the definition of EGC, the regional LNM is one of the most important prognostic factors in EGC. One report of trends in Incident, Management, and Survival in a Well-Defined French Population of Early Gastric Cancer demonstrated that the 5-year net survival was 50% in node-positive patients and 85% in node-negative patients (11). As a result, the lymph node positiveness decides the survival of EGC and whether the additional lymphadenectomy is required (12).

The previous studies confirmed that several risks such as tumor size, invasion depth, ulceration, histological types, and lymph vascular invasion were related with LNM in EGC (13–16). Even a few of research based on these factors constructed traditional scoring to evaluate the probability of LNM in EGC after the endoscopic resection (17, 18). According to the previous study, the percentage of actual lymph node positive after additional surgery of EGC is about 10% based on these scorings (19, 20). Certainty, the accuracy of these scorings is necessary more data of clinical practice.

Artificial intelligence (AI) is an advanced technology that has been used in many fields such as in industry, agriculture, navigation, driverless car, and healthcare (21–23). AI is a subfield of computer science that emphasizes the design of intelligent systems that can learn from the data and make decisions and predictions accordingly (24). Among many branches of AI, machine learning (ML) and deep learning (DL) are two major parts of all (25). ML is a mathematical AI algorithm automatically built from given data to predict precise outcomes in uncertain conditions without being explicitly programmed (26).

Currently, ML has been used to the wide area of medicine; the potential ability of ML can improve the efficiency and accuracy of clinical work, such as analyzing millions of clinical data to create prognostic, screening, and diagnostic models (27–29). ML has a satisfactory to excellent accuracy for predicting cancer, such as the oral cavity cancer; the accuracy prediction of cervical LNM was about 90% (30) and, in the early stage of colorectal cancer, ML model showed superior performance compared with conventional criteria in predicting LNM (31). In EGC, few studies have established predictive models with ML. For the reasons stated above, in the present multicenter study, we aim to study EGC with the additional surgery to evaluate the factors such as LNM better to construct a robust prediction model with ML to provide another evaluation method to choose the suited treatment for patients.

Material and methods

Study design

This was a multicenter, retrospective analysis. The cohort I was obtained from the Sixth Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China), which was used to construct the prediction models, and the cohort II as the external validation date was from the University Hospital Virgen del Rocio (Seville, Spain), which was performed to verify the ability of models. The present study was approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-Sen University and the

University Hospital Virgen del Rocio; the approval number is E2021197.

Study population

The authors retrieved EGC patients who only received additional gastrectomy from the electronic medical record system of the Sixth Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China). All patients were recruited from January 2012 to March 2021. After screening, a total of 373 records were found, and 68 patients met any of the exclusion criteria; then, 305 cases with pathologically confirmation of T1a/T1b stage were included in the study and underwent additional gastrectomy with systemic lymphadenectomy (D2) (Figure 1). The exclusion criteria in this study were as follows: (1) patients who have received previous neoadjuvant therapy, (2) patients that present two or more gastric and/or other primary cancer type, (3) patients' previous history of cancer or remnant gastric cancer, (4) patients with distant metastasis, and (5) incomplete preoperative examinations (variables with >25% of missing information), including blood analysis, gastroscopy pathological reports, and/or pathological results. These exclusion criteria were used for both cohort I and cohort II by the ML models. For the external validation, a cohort of 35 patients who underwent additional gastrectomy with standard lymphadenectomy at the University Hospital Virgen del Rocio (Seville, Spain) between January 2014 and December 2020 was recruited (Figure 1).

Clinicopathological evaluation

The medical records for blood analysis, gastroscopy, and pathological reports for each patient were reviewed for the analysis. From the blood analyses data were gathered tumor markers such as CEA, CA199, CA125, CA153, and AFP. Gastroscopy data were collected from the report, which included the location of the tumor. The pathological results provided information about invasion depth (T1a/T1b), histologic type, Lauren classification, tumor size, and ulceration. The clinical characteristics of the patients, including sex, age, body mass index (BMI), and personal pathological history were also collected.

Statistical analysis and ML models

Association analysis

According to the clinicopathological results, the univariate analysis was performed on all variables; all data sets were divided into two groups according to the lymph nodes positiveness. Association analysis was applied to all variables individually, categorical variables with expected frequency greater than 5 in

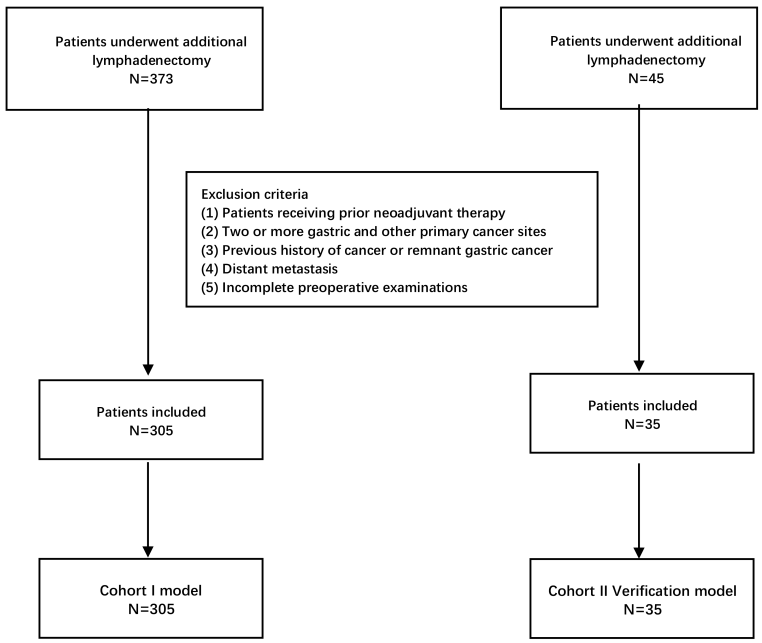

FIGURE 1
Flowchart of patients included in the study for construction models and external validation models according to the inclusion and exclusion criteria.

the LNM group and the non-LNM group were tested by chi-square test, and categorical variables with expected frequency less than 5 in the LNM group or non-LNM group were tested by Fisher's exact test. Continuous variables were tested by the T student test (the *p*-value greater than 0.05 in Shapiro–Wilk test and Levine's test) and the Mann–Whitney test. The chi-square test or Fisher's exact test was also used for tumor markers after categorization into binary variables using the following cutoff points set as normal range (37 U/ml for CA19-9, 5 ng/ml for CEA, 35 U/ml for CA125, 32.4 U/ml for CA153, and 8.78 ng/ml for AFP) (32).

ML models

After a comprehensive review of different ML prediction algorithms reported in the literature, compared the scalable, flexible, accurate, and relatively fast, five types of supervised ML classifiers were selected to provide for the establishment the prediction model in EGC (33–37). These models were the logistic regression classifier (LRC), linear support vector classifier (Linear SVC), Gaussian process classification (GPC), and two gradient boosting methods extreme gradient boosting (XGBoost) and light gradient boosting machine (LightGBM).

LRC is a classification model rather than regression model, which is a simple and more efficient method for binary and linear classification problems; it is a classification model that is very easy to realize and achieves excellent performance with linearly separable classes (38). Linear SVC was performed to obtain method based on support vector classifier (SVM). SVM is a widely used alternative to softmax for classification and is used for both linear and nonlinear classification by changing the kernel functions utilized (39). GPC can naturally give predicted probabilities for classification problems that require tuning of the kernel functions (40). It was used for complex non-parametric ML algorithms for classification and regression (41). XGBoost and LightGBM were considered among the most recent and efficient ML-based prediction algorithms (42). The XGBoost model, which can handle both regression and classification problems, is widely used by data scientists to achieve state-of-the-art results (43). LightGBM is a gradient learning framework based on the decision tree and the idea of boosting (44). Its major difference from the XGBoost model is that it uses histogram-based algorithms to speed up the training process, reduce memory consumption, and employ a leaf-wise growth strategy with depth constraints (37). The original codes of these five algorithms, which were performed in this study, were based on Python 3.9 and scikit-learn 1.0 (45).

Feature selection and construction the ML methods

For ML approach, all features included in the model were determined by the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the Least Absolute Shrinkage and Selection Operator (LASSO), which were widely used for finding the best features for models (46, 47). According to the previous study (48), all variables were included for feature selection in the LASSO binary logistic regression model, in the AIC scores, and in the BIC scores for all possible combinations, which with $p < 0.15$ in the univariable analysis were predefined as the cutoff and the factors were reported from previous study in the LASSO binary logistic regression model, in the AIC scores, and in the BIC scores for all possible combinations. The final features were applied to establish ML models depending on these three methods (AIC, BIC, and LASSO). The statistical analyses were performed using SPSS® version 26 (IBM SPSS Statistics for Macintosh) and R Studio (Integrated Development for R. RStudio, PBC, Boston, MA, version 4.0.5).

All selected categorical features were transformed into dummy variables. Then, all features were used to construct the ML models to predict LNM. All models used fivefold cross-validation on both cohort I and cohort II. All models were evaluated by the receiver operating characteristic curve (AUC) and optimized by the grid search; the Bayesian method was used to improve the ability of model. For LRC and Linear SVC models, the importance of features was calculated by their weight coefficients. For XGBoost and LightGBM, the importance of features was also plotted. All models were constructed and analyzed by Python (version 3.9.4). All files used for model construction have been placed in the supplement.

External validation

All ML models were verified by external validation data and accuracy; AUC, Brier score, F1 score sensibility, specificity, and 95% ICs were estimated using the bootstrap method. Other bioinformatic approaches such as confusion matrices, ROC curves, and calibration curves were used in the present analysis. The groups that exhibited a high-risk were established by predictive probability, and their relative odds ratios were calculated.

Results

Clinicopathological variables associate with lymph node metastasis

The primary cohort (cohort I) included a total of 305 patients, of whom 69 patients (22.6%) had LNM according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system (49). The classification of tumor size was based on the eCura system of the Japanese Gastric Cancer Treatment Guidelines ed. 2018 (50). The tumor size was divided into three groups (≤ 2cm, 2–3 included, > 3cm). Their demographic and clinicopathological characteristics are shown

in Table 1. In univariable analysis (in the association analysis), "age" was the only continuous variable that showed statistically significant differences between both groups ($t = 2.64$, $P = 0.009$). After categorization, this variable was divided into five groups based on the risk of cancer associated to age from National Cancer Institute of US (< 30 years, 30–40 years, 40–50 years, 50–60 years, and > 60 years) (51). The chi-square test showed statistically significant differences between all five groups ($\chi^2 = 20.991$, $P < 0.001$). The biomarkers such as CEA ($U = 9006$, $P = 0.178$) and CA125 ($U = 7123.5$, $P = 0.114$) met the variable filter criteria, but their binary form (normal *vs.* high) were not statistically significant ($P = 1.0$ and $P = 0.428$, respectively). Other categorized variables such as invasion depth ($\chi^2 = 17.377$, $P < 0.001$), histologic type ($\chi^2 = 7.715$, $P = 0.005$) and LAUREN

TABLE 1 Clinicopathologic characteristics of patient samples included in the present study.

Variable	LNM negative ($N = 236$)	LNM positive ($N = 69$)	*P*-value
Age (year, mean±std)	59.0 ± 11.4	54.87 ± 12.5	**0.009**[a]
Gender			0.697[C]
Male (*n*, %)	135 (57.21%)	37 (53.62%)	
Female (*n*, %)	101 (42.79%)	32 (46.38%)	
BMI (mean ± std)	22.69 ± 3.44	22.62 ± 2.83	0.881[a]
DM			0.764[d]
Yes (*n*, %)	12 (5.08%)	4 (5.79%)	
No (*n*, %)	224 (94.92%)	65 (94.21%)	
HTA			0.321[C]
Yes (*n*, %)	31 (13.14%)	13 (18.84%)	
No (*n*, %)	205 (86.86%)	56 (81.16%)	
Tumor location			0.119[C]
Fundus (*n*, %)	31 (13.14%)	3 (4.35%)	
Body (*n*, %)	52 (22.03%)	18 (26.09%)	
Antrum (*n*, %)	153 (64.83%)	48 (69.56%)	
Depth of invasion			**<0.001**[C]
T1a (*n*, %)	131 (55.51%)	18 (26.09%)	
T1b (*n*, %)	105 (44.49%)	51 (73.91%)	
Histologic type			**0.005**[C]
Undifferentiated type (*n*, %)	147 (62.29%)	56 (81.16%)	
Differentiated type (*n*, %)	89 (37.71%)	13 (18.84%)	
LAUREN classification			**0.004**[C]
Diffuse type (*n*, %)	93 (39.41%)	34 (49.28%)	
Intestinal type (*n*, %)	95 (40.25%)	13 (18.84%)	
Mixed type (*n*, %)	48 (20.34%)	22 (31.88%)	
Tumor size			0.166[C]
2–3(included) cm (*n*, %)	58 (24.58%)	19 (27.54%)	
>3 cm (*n*, %)	38 (16.10%)	17 (24.64%)	
≤2cm (*n*, %)	140 (59.32%)	33 (47.82%)	
Ulceration			0.053[C]
Negative (*n*, %)	165 (69.92%)	39 (56.52%)	
Positive (*n*, %)	71 (30.08%)	30 (43.48%)	
AFP (median, range)	2.47 (0.95-14.37)	2.74 (0.84-107.97)	0.279[b]
CA125 (median, range)	9.55 (2.7-130.7)	10.6 (3.1-191.7)	0.114[b]
CA153 (median, range)	7.2 (1.9-27.1)	10.6 (3.1-19.6)	0.858[b]
CA199 (median, range)	4.90 (2-115.14)	5.11 (2.0-338.54)	0.743[b]
CEA (median, range)	2.08 (0.51-23.59)	1.87 (0.53-9.88)	0.178[b]

[a]Independent two-sample t-test.
[b]Mann–Whitney U test.
[c]X^2 test with Yates' continuity correction.
[d]Fisher' s exact test.
The bold values means these variables show statistically significant differences between both groups.

classification (χ^2 = 11.260, P = 0.005) were statistically significant, and the presence of ulcer presented a high trend toward significance (χ^2 = 3.741, P = 0.053). Nevertheless, tumor size (χ^2 = 3.590, P = 0.166) and tumor location (χ^2 = 4.260, P = 0.119) exhibited no association with LNM.

Selected variables

A total of seven variables were included as potential risk factors in the prediction model, which the p-values in univariable analysis were less than 0.15 (Table 1 and Figure 2A). CEA and tumor size have been reported from the previous study, which were related with LNM in EGC (54, 55), but CA125 was discarded from the model by lack of data in the cohort II. In the LASSO method, the including variables were exhibited a minimum mean squared error (MSE) by five cross-validation folds, which were the invasion depth, histologic type, ulceration, tumor location, tumor size, Lauren classification, and age. The variables included which with standard error of MSE contained the age and invasion depth (Figure 2B). There are five variables in the group; the minimum AIC score was 299.08 with five variables, which were the depth of invasion, histologic type, the presence of ulcer, tumor size, and age (Figure 2C) and, in the minimum, BIC score was 301.07 and was obtained with four variables, which were the depth of invasion, the presence of ulcer, tumor size, and age (Figure 2D). Finally, the features selected with minimum mean squared error (MSE) in LASSO were applied to establish the prediction ML models. Finally, seven variables, namely, age, tumor location, histologic type, the LAUREN classification, tumor size, invited depth, and ulceration (positive/negative), were included in at least one of these methods. These seven variables were used to training the ML models.

Once the variables were selected with LASSO, Table 2 was assessed to compare detailed clinic-pathological characteristics

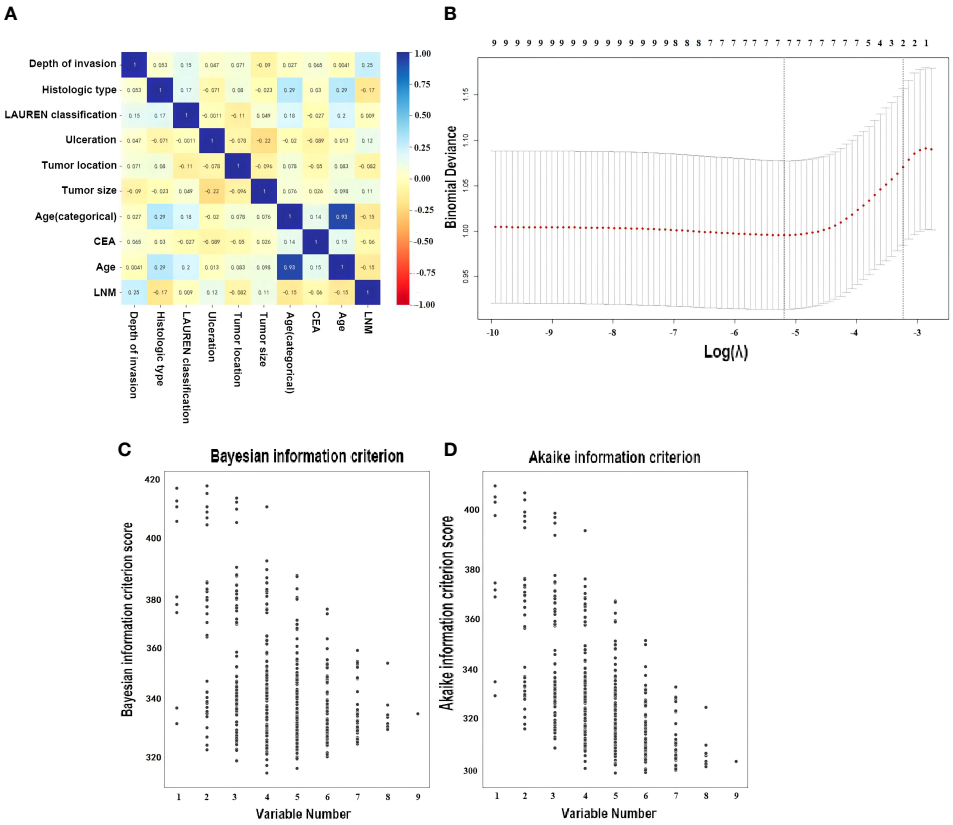

FIGURE 2
Optimal variable combination selection. **(A)** Correlation matrix of variables. **(B)** Result by Least Absolute Shrinkage and Selection Operator (LASSO). Here, the partial likelihood deviance (binomial deviance) curve was plotted in log(λ) scale. Dotted vertical lines were drawn at the values of log(λ) with minimum mean squared error (MSE) and the maximum log(λ) of one SE of the minimum MSE. The best features were selected with minimum mean squared error (MSE) from the five cross-validation folds, with lambda value 0.00558, log(λ) is −5.19. One SE of the minimum MSE with lambda value 0.03936, log(λ) is −3.24. **(C)** Dot plot performed by Bayesian Information Criterion (BIC) for all possible models (disregarding potential transformations and interactions) employing none, any or all of the seven selected risk factors, a lower BIC indicates a better fit (52). **(D)** Dot plot performed by Akaike Information Criterion (AIC), a lower AIC indicates a better fit (53).

between the cohort I and cohort II groups. Both cohort I and cohort II had a ratio of LNM negative/positive similar, 3.42 and 3.38, respectively.

ML models can predict lymph node metastasis

The statistical weigh of the different variables for the light gradient boosting machine classifier (LightGBM), extreme gradient boosting classifier (XGBoost), LRC, and linear support vector machine classifier (Linear SVC) are shown in Figure 3. Tumors invaded the submucosal (T1b), intestinal type, age < 30, and the presence of ulcer were the four factors with the highest statistical power to establish these four models.

The confusion matrices for the five classifiers in the cohort I and cohort II with the percentage of their true label are displayed in Figure 4. This corresponds to specificity, false positive rate (FPR), false negative rate (FNR), and sensibility in each subplot. Both Linear SVC and LightGBM presented a better sensibility in the models; the Linear SVC showed a robust performance in sensibility, 0.71 in cohort I and 0.75 in cohort II. The logistic regression, XGBoost, and the Gaussian process classifier performed a better specificity. Concerning the sensibility, in the Logistic Regression and XGBoost were improved in cohort II, both with a sensibility of 0.5, equal a completely random decision. The Gaussian process classifier was the most stable model in these five models, and the best performance in specificity, with 0.99 in the cohort I, and 0.93 in the cohort II.

The discrimination and calibration of the five models in the cohort I and cohort II were shown in Figure 5. For testing models of ML, each model had better ability to the prediction, the area under the curve (AUC) values of all algorithms were closed to 0.8 between the cohort I and cohort II, even the Gaussian process classification had exceeded this value in both set (0.816, 95% CI 0.813–0.819 *vs.* 0.803, 95% CI 0.799–0.808). However, compared with the different values of AUC between the cohort I and cohort II for all models, the XGBoost (0.781 *vs.* 0.804) and the Gaussian process classification (0.816 *vs.* 0.803) had tiny difference in both sides. It meant that these two models

TABLE 2 Clinicopathologic characteristics for established the prediction model between cohort I and cohort II.

Variable	Cohort I		Cohort II	
	LNM negative (*N* = 236)	LNM positive (*N* = 69)	LNM negative (*N* = 27)	LNM positive (*N* = 8)
AGE (years)				
age < 30 (*n*%)	1 (0.42)	5 (7.25)	0 (0.00)	0 (0.00)
age 30–40 (*n*%)	20 (8.47)	3 (4.35)	1 (3.70)	0 (0.00)
age 40–50 (*n*%)	28 (11.86)	16 (23.19)	2 (7.41)	1 (12.50)
age 50–60 (*n*%)	75 (31.78)	22 (31.88)	1 (3.70)	1 (12.50)
age > 60 (*n*%)	112 (47.47)	23 (33.33)	23 (85.19)	6 (75.00)
TUMOR LOCATION				
Fundus (*n*%)	31 (13.14)	3 (4.35)	0 (0.00)	2 (25.00)
Body (*n*%)	52 (22.03)	18 (26.09)	12 (44.44)	2 (25.00)
Antrum (*n*%)	153 (64.83)	48 (69.56)	15 (55.56)	4 (50.00)
HISTOLOGIC TYPE				
Undifferentiated (*n*%)	147 (62.29)	56 (81.16)	12 (44.44)	4 (50.00)
Differentiated (*n*%)	89 (37.71)	13 (18.84)	15 (55.56)	4 (50.00)
LAUREN				
Diffuse (*n*%)	93 (39.41)	34 (49.28)	7 (25.93)	3 (37.50)
Intestinal (*n*%)	95 (40.25)	13 (18.84)	20 (74.07)	3 (37.50)
Mixed (*n*%)	48 (20.34)	22 (31.88)	0 (0.00)	2 (25.00)
TUMOR SIZE (cm)				
2–3 (include) (*n*%)	58 (24.58)	19 (27.54)	7 (25.93)	5 (62.50)
> 3 (*n*%)	38 (16.10)	17 (24.64)	10 (37.04)	3 (37.50)
≤ 2 (*n*%)	140 (59.32)	33 (47.82)	10 (37.04)	0 (0.00)
DEPTH OF INVASION				
T1a (*n*%)	131 (55.51)	18 (26.09)	8 (29.63)	0 (0.00)
T1b (*n*%)	105 (44.49)	51 (73.91)	19 (70.37)	8 (1.00)
ULCERATION				
Negative (*n* %)	165 (69.92)	39 (56.52)	11 (40.74)	1 (12.50)
Positive (*n* %)	71 (30.08)	30 (43.48)	16 (59.26)	7 (87.50)

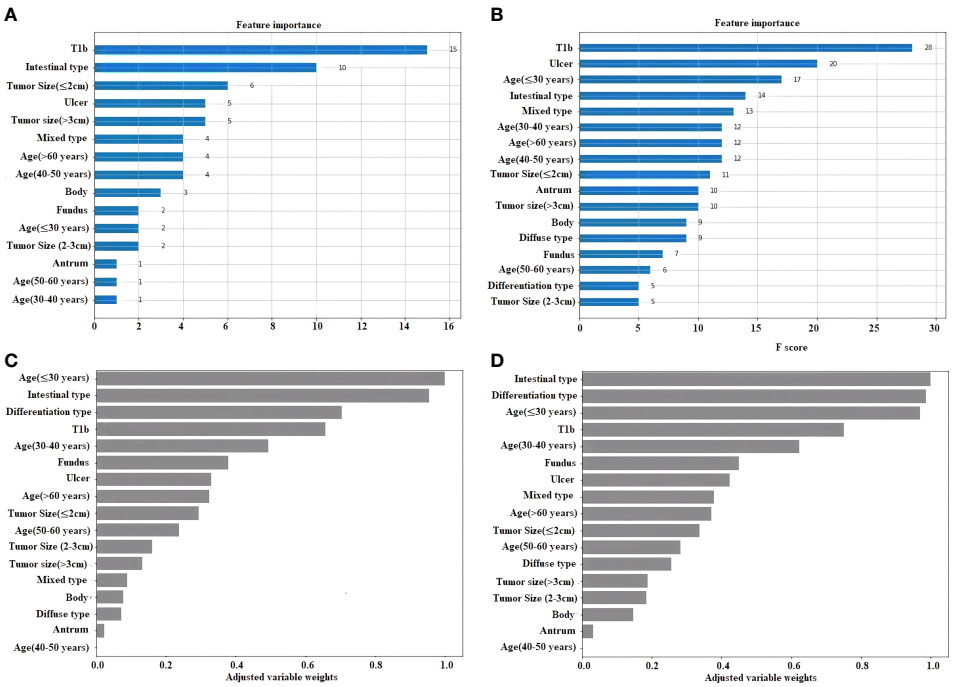

FIGURE 3
Feature importance plot for the 4 ML. **(A)** Light gradient boosting machine classifier (LightGBM). **(B)** Extreme gradient boosting classifier (XGBoost). **(C)** Logistic regression classifier. **(D)** Linear support vector machine classifier (Linear SVC).

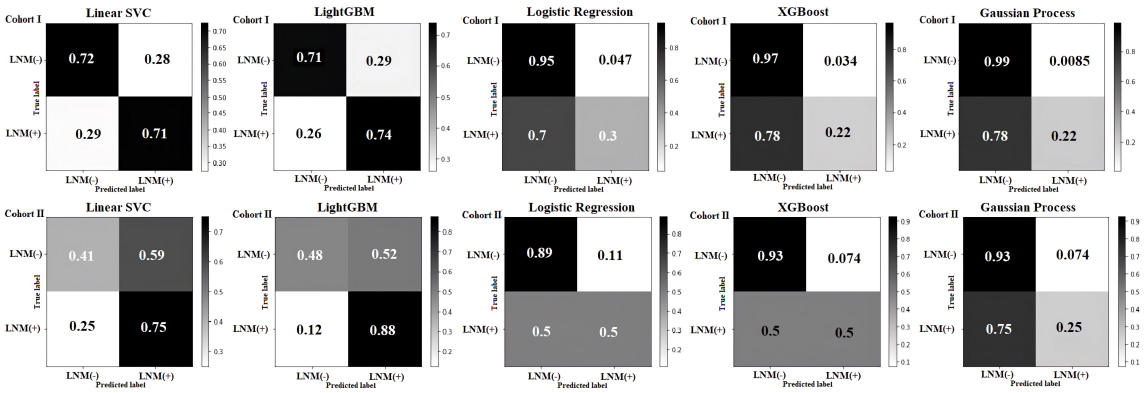

FIGURE 4
Confusion matrix of the cohort I and the cohort II in five machine learning models. In each subplot, the specificity, false positive rate (FPR), false negative rate (FNR), and sensibility were shown from top left to bottom right, respectively.

had the almost same ability for the prediction in cohort I and cohort II (Figures 5A, E). The 95% CI of the calibration belt in both cohort I and cohort II did not cross the diagonal bisector line, which suggests that the prediction models had a strong concordance between both groups and further indicates the five models demonstrate an accurate prediction potential in both groups. The XGBoost and the Gaussian process classification were closer the dotted line to the ideal line, these two models had the better the predictive accuracy (Figures 5F–J).

Table 3 shows the prediction performance of five ML classifiers for cohort I and cohort II. The XGBoost classifier and Gaussian process classification demonstrated the best performance due to there was a little difference between the cohort I and cohort II: the cohort I′s specificity 96.7% (95% CI

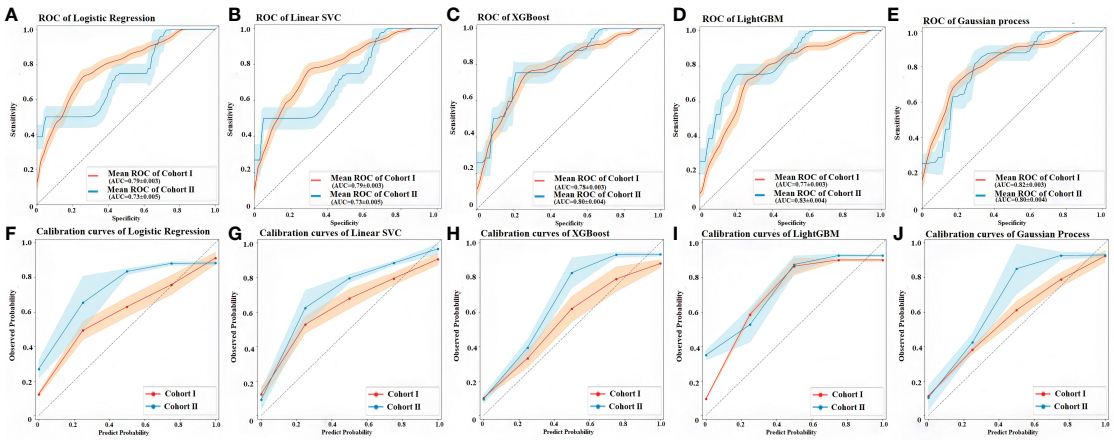

FIGURE 5
Discrimination and calibration performance of the 5 models. **(A)** ROC curves of the Logistic regression classifier in the cohort I and cohort II, respectively (AUC=0.788, 95% CI 0.785–0.790 *versus* 0.732, 95% CI 0.727–0.738). **(B)** ROC curves of the linear support vector machine classifier (Linear SVC) in the cohort I and cohort II, respectively (AUC=0.786, 95% CI 0.783–0.789 *versus* 0.736, 95% CI 0.731–0.741). **(C)** ROC curves of the in the extreme gradient boosting classifier (XGBoost) in the cohort I and cohort II, respectively (AUC = 0.781, 95% CI 0.778–0.784 *versus* 0.804, 95% CI 0.799–0.809). **(D)** ROC curves of the Light gradient boosting machine classifier (LightGBM) in the cohort I and cohort II, respectively (AUC = 0.766, 95% CI 0.763–0.769 *versus* 0.830, 95% CI 0.826–0.835). **(E)** ROC curves of the Gaussian process classification in the cohort I and cohort II, respectively (AUC = 0.816, 95% CI 0.813–0.819 *versus* 0.803, 95% CI 0.799–0.808). The light orange area and blue area represent the 95% CIs in cohort I and cohort II, respectively. 500 Bootstrap resamples were used to calculate a relatively corrected AUC and 95% CI. Calibration curves of five models in the cohort I and cohort II are shown in figures from **(F–J)** The 45° dashed line represents a perfect prediction, the orange lines represent the predictive performance of the model in the cohort I, and the blue lines represent the predictive performance of the model in the cohort II. The closer the dotted line to the ideal line, the better the predictive accuracy of the model is (56). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

96.5–96.8%) and 99.1% (95% CI 99.1–99.2%); accuracy 79.6% (95% CI 79.4–79.8%) and 81.5% (95% CI 81.3–81.7%); AUC 78.1% (95% CI 77.8–78.4%) and 81.6% (95% CI 81.3–81.9%), the cohort II´s specificity 92.6% (95% CI 92.3–92.8%) and 92.6% (95% CI 92.3–92.8%); accuracy 82.6% (95% CI 82.3–82.8%) and 77.1% (95% CI 76.8–77.4%); AUC 80.4% (95% CI 79.9–80.9%) and 80.3% (95% CI 79.9–80.8%), respectively. The sensibility and F1 score values were also demonstrated in this table. The F1 score can be interpreted as a harmonic mean of the precision and recall, where an F1 score reaches its best value at 1 and worst score at 0 (57) although, in these five models, the F1 score was already between in 0.33 and 0.57. A brier score was a way to verify the accuracy of a probability forecast. A probability forecast refers to a specific event. The best possible Brier score is 0, for total accuracy. The lowest possible score is 1, which means the forecast was wholly inaccurate (58). In this study, all of the models had the Brier score, which was less than 0.25.

The decision curve of the XGBoost and Gaussian Process Classification models had a more comprehensive net benefit threshold probability range in the cohort I, although these were no statistical differences in the cohort II (Figure 6). Analysis showed that when the predictive criticism was > 0 in the XGBoost model and Gaussian process classification in the cohort I, the models added more net benefit than “no patient with LNM” or “all patients with LNM” scheme (Figure 6A). The predictive criticism ranged from 0 to 0.357 of the XGBoost model and 0 to 0.293 of the Gaussian process classification in the cohort II, the models added more net benefit than “no patient with LNM” or “all patients with LNM” scheme (Figure 6B).

Subsequently, the predicted probability was categorized as low, medium, and high risk. Table 4 shows the odds ratio (OR) value of LNM prediction for each model. When comparing the different levels of risk, Linear SCV classifier, XGBoost classifier, and Gaussian process classification showed the highest capacity for the prediction due to the positive gradient increasing in different levels. The medium risk of Linear SCV classifier was 3.5 times higher than the low risk, and the high risk was seven times than the low risk. The Gaussian Process has 5.46 and 16.67 times comparing the medium and high risk with low risk. Even though the medium risk of XGBoost showed no statistically significant increasing compared with the low risk (1.67 *vs.* 1). LRC demonstrated the negative gradient comparing the high and medium risk (4.5 *vs.* 4.8), and LightGBM showed the negative gradient in medium and low risk (0.89 vs 1).

Discussion

With the development of minimally invasive endoscopic technology, ESD is the gold standard to treat the EGC (7, 50, 60), due to the benefit such as minor trauma, quick recovery, and a better quality of life could be improved after the treatment (61, 62).

TABLE 3 Validation performance for the prediction of LNM of EGC by using five machine learning classifiers.

Machine learning	Sensibility (95% CI)	Specificity (95% CI)	F1 Score (95% CI)	Accuracy (95% CI)	AUC (95% CI)	Brier (95% CI)
Linear SVC						
Cohort I	0.711 (0.707–0.716)	0.727 (0.724–0.729)	0.538 (0.534–0.542)	0.723 (0.720–0.725)	0.786 (0.783–0.789)	0.207 (0.204–0.211)
Cohort II	0.748 (0.740–0.755)	0.408 (0.404–0.412)	0.398 (0.393–0.403)	0.486 (0.482–0.489)	0.736 (0.731–0.741)	0.225 (0.223–0.227)
Logistic Regression						
Cohort I	0.302 (0.297–0.308)	0.955 (0.953–0.956)	0.413 (0.407–0.419)	0.806 (0.804–0.808)	0.788 (0.785–0.790)	0.189 (0.186–0.191)
Cohort II	0.500 (0.492–0.509)	0.890 (0.887–0.892)	0.531 (0.524–0.538)	0.798 (0.795–0.801)	0.732 (0.727–0.738)	0.235 (0.232–0.237)
XGBoost						
Cohort I	0.215 (0.210–0.220)	0.967 (0.965–0.968)	0.323 (0.317–0.329)	0.796 (0.794–0.798)	0.781 (0.778–0.784)	0.145 (0.143–0.146)
Cohort II	0.500 (0.492–0.509)	0.926 (0.923–0.928)	0.568 (0.561–0.575)	0.826 (0.823–0.828)	0.804 (0.799–0.809)	0.172 (0.171–0.174)
LightGBM						
Cohort I	0.739 (0.734–0.743)	0.708 (0.705–0.711)	0.540 (0.536–0.544)	0.714 (0.712–0.717)	0.766 (0.763–0.769)	0.234 (0.233–0.236)
Cohort II	0.880 (0.874–0.886)	0.478 (0.474–0.482)	0.480 (0.475–0.485)	0.566 (0.563–0.569)	0.830 (0.826–0.835)	0.245 (0.243–0.247)
Gaussian Process						
Cohort I	0.214 (0.209–0.219)	0.991 (0.991–0.992)	0.344 (0.337–0.350)	0.815 (0.813–0.817)	0.816 (0.813–0.819)	0.139 (0.138–0.140)
Cohort II	0.254 (0.246–0.262)	0.926 (0.923–0.928)	0.333 (0.324–0.342)	0.771 (0.768–0.774)	0.803 (0.799–0.808)	0.185 (0.184–0.187)

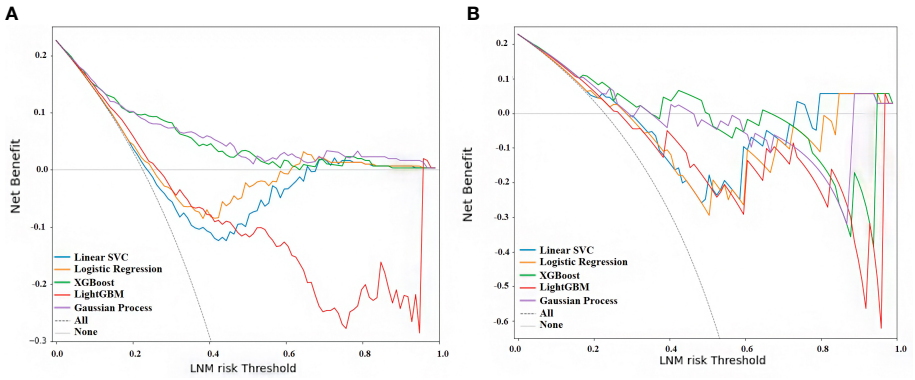

FIGURE 6
Decision curve analysis for all five models. **(A)** Curve of cohort (I) **(B)** Curve of cohort II. The x-axis measures the net benefit, and the y-axis shows the LNM risk threshold. The blue line represents the linear support vector machine classifier (Linear SVC), the orange line the logistic regression classifier, the green line the extreme gradient boosting classifier (XGBoost), the red line the light gradient boosting machine classifier (LightGBM), the purple line the Gaussian process classification, the gray solid line the assumption that no patient with LNM, and the dashed line represents all patients with LNM (59).

However, the LNM is a problem that depends on whether receive or not an additional lymphadenectomy. The traditional methods of predicting LNM could have certain limitations, in recent studies the EGC patients with only the evaluation of clinicopathological characteristics after ESD needed to perform additional surgery due to having a high risk of LMN; however, actually, the risk of LNM was approximately 10% after the lymphadenectomy (19, 20, 63). Therefore, a good predictive

TABLE 4 Odds ratio and confidence intervals between different risk group in five machine learning classifiers.

OR values (95% CI)	Linear SVC	Logistic regression	XG Boost	Light GBM	Gaussian process
Low risk	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Medium risk	3.5 (3.15–3.89)	4.8 (4.32–5.34)	1.67 (1.54–1.81)	0.89 (0.79–0.99)	5.46 (4.94–6.03)
High risk	7.0 (6.35–7.71)	4.5 (4.08–4.96)	10.0 (9.26–10.79)	4.0 (3.63–4.41)	16.67 (15.10–18.39)

Range of predicted probability: low risk (0–0.25); medium risk (0.25–0.5); high risk (>0.5).

method can predict LNM in nearby 80% and help to reduce unnecessary surgery and improve the patient's quality of life. ML had been used broadly in medicine, since it can help to improve the accuracy of clinical prediction (28, 64, 65). In this study, we found that the ML models were the most important benefit of improving predictive accuracy to detect the LNM in EGC.

According to the feature selection, we found that the risk factors related to LNM such as age; the presence of ulceration, tumor size, and depth of invasion; the histologic tumor type; the tumor location; and Lauren classification were common in each model (AIC, BIC, and LASSO) (Figure 2). This is almost consistent with the ranking of variables importance in the results of ML models, although the order was different (Figure 3). Previous studies had been considered that these factors were related to the LNM in EGC (13, 66). On the other hand, the age was the risk that was included in these prediction models (Figure 3), although the age was not contained in the traditional evolution scale (50), but age-related studies involving many carcinoma patients have yielded some relevant results (67, 68). Perhaps, in the future, based on the ML models, we can find more factor combinations that would be constructed the optimized group that influences the LNM in EGC. This fact can provide a new solution to find the related factors and design new ML models in clinical research for prediction.

Another point in this study was the use of ML for the prediction of LNM. Here, we found that the Linear SVC and Light gradient boosting classifier (LightGBM) were the best models to detect the actual positive cases, although the rest three models presented excellent abilities to detect the actual negative cases (Figure 4). According to the predicted probability, the XGBoost classifier and Gaussian process classification had the best predictive accuracy of the model than the others. This is probably due to the random sampling results that were closer to the ideal line (Figure 5). Furthermore, they had a more comprehensive net benefit threshold probability range in the cohort I, which that meant for the patient with LNM who was predicted by XGBoost model and Gaussian process; the additional treatment could be had more benefit for them (Figure 6). In the predicted probability among different risk groups, the Linear SVC, XGBoost classifier, and Gaussian process had a certain degree of discrimination. The OR value was obviously increased among low, medium, and high risk, which were applied with the Linear SVC, and Gaussian process. This means that these two models are better to detect the risk in different groups (Table 4). Thus, as can be observed, each model has its own characteristics and advantages in prediction, but Gaussian Process shows the best comprehensive predictive ability in this study. Perhaps, for the prediction of the LNM in EGC, we could combine multiple models to increase prediction ability. Xiao Y. et al. demonstrated that the ML methods have been more and more widely used in cancer prediction. However, no individual method exceeded the others, and a combination of models could imply an optimal final prediction (69).

It is undeniable that this study also has certain limitations. First, the model was constructed using a retrospective cohort; therefore, a prospective data set could be appropriate to improve the ability of the prediction model; perhaps we can find more risks that could be related to LNM. In addition, all preoperative examination results were obtained from reports; therefore, information bias was unavoidable. This study has been performed with a limited sample size, especially cohort II. However, results differed slightly between the cohort I and cohort II, which implies not only a different origin (China and Spain) but also a different ethnicity. In future work, we will make a prospective trial that includes more variables, such as biomarkers, and supplement with more predictive models to improve the prediction ability.

In conclusion, we established five commonly used ML models to predict LNM in EGC; according to our results, machine learning can be used to detect high-risk LNM in EGC, especially the Gaussian Process Classification had the best comprehensive predictive ability. This could be applied to indicate that additional lymphadenectomy is necessary after the endoscopic resection in EGC. From another point of view, machine learning could provide a new solution to find the related factors in clinical research for prediction of LNM in EGC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

Study concept and design: TY, JM-U, JL, and SM-C; Acquisition of data: TY, IA, and XJ; Build Models' code: CL; Analysis and interpretation: TY, WL, YX, XJ, and YZ; Study supervision: SM-C and ZY. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1023110/full#supplementary-material

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Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Giovanni Cochetti,
University of Perugia, Italy
Ahmed Farag,
Cairo University, Egypt

*CORRESPONDENCE
Hao Sun
sunhao68@sina.com

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Effects of wound infection on prognosis after laparoscopic abdominoperineal resection of rectal cancer

Wang Huang[1], Zheng-qiang Wei[2], Yu-hao Qiu[2], Gang Tang[2] and Hao Sun[1]*

[1]Department of Gastrointestinal Surgery, Chongqing University Cancer Hospital, Chongqing, China, [2]Department of Gastrointestinal Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: In two facilities in Chongqing, this research sought to retrospectively evaluate the effects of perineal wound infection on survival after laparoscopic abdominoperineal resection (LAPR) of rectal cancer.

Methods: To obtain clinical information on patients who underwent LAPR between January 2013 and December 2021, we performed a multicenter cohort study. A total of 473 patients were enrolled: 314 in the non-infection group and 159 in the group with perineal infection. The general data, perioperative conditions, and tumor outcomes between groups were analyzed. The infection rates, recurrence rates, and survival rates of the two centers were compared.

Results: The age, height, weight, body mass index (BMI), preoperative complications, preoperative treatment, and intraoperative conditions of patients in the LAPR infection group were not statistically different from those in the non-infection group. The percentage of men, typical postoperative hospital stay, length of initial postoperative therapy, and recurrence and metastasis rates were all considerably higher in the infection group than those in the non-infection group. Wound infection was an independent factor affecting tumor recurrence and metastasis after LAPR as well as an independent factor shortening patient survival time according to multivariate analysis. The incidence of wound infection, the rate of recurrence, and the rate of mortality did not vary significantly across sites.

Conclusion: Wound infection after LAPR increases the mean postoperative hospital stay, prolongs the time to first postoperative treatment, and decreases

the disease-free survival (DFS) and overall survival (OS). Therefore, decreasing the rate of LAPR wound infection is expected to shorten the postoperative hospital stay and prolong the patient DFS and OS. Patients with postoperative infection may require intensive adjuvant therapy.

KEYWORDS

rectal cancer, wound infection, cancer recurrence, cancer metastasis, laparoscopic abdominoperineal resection (LAPR)

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignant tumors. Nearly 90% of patients with CRC undergo tumor resection (1). The most frequent postoperative consequence of CRC is surgical site infection (SSI), including wound infection, anastomotic leakage, and abdominal infection, with an infection rate as high as 45% (2). SSI leads to long postoperative hospital stays and increases the use of postoperative antibiotics, reoperation rate, and psychological stress in patients; in addition, SSI can lead to increased health care costs (3–5). Moreover, SSI decreases disease-free survival (DFS) and overall survival (OS) (6, 7). Rectal anastomotic leakage has been linked to a higher risk of tumor recurrence and shorter OS according to a meta-analysis (8). The relationship between postoperative wound infection, an important component of SSI, and the prognosis of CRC has not yet been reported.

Importantly, 40% of patients with rectal cancer must undergo abdominoperineal resection (APR) (9) despite progress in surgical techniques and rectal cancer treatments. Compared with other surgical methods, APR has a higher wound infection rate. After wound infection, the prognosis time is long. Perineal wound infection, in severe cases, may show wound nonunion or chronic sinus formation, thus resulting in long-term chronic inflammation. Related research has shown that tumor incidence and growth are significantly influenced by inflammation. Rectal anastomotic leakage leads to an increase in the local recurrence rate of tumors after surgery, which may be caused mainly by long-term local chronic inflammatory stimulation. For patients with postoperative perineal incision infection, a contaminated incision and poor local blood supply to the wound may lead to long healing times and long-term inflammation at the site of the tumor resection. Whether this inflammatory state might also increase the local recurrence rate and decrease the DFS and OS of patients was unknown.

This study was aimed at investigating the relationships between perineal wound infection and tumor recurrence, metastasis, and survival after laparoscopic abdominoperineal resection (LAPR) to serve as a standard of comparison for the clinical diagnosis and management of rectal cancer.

Patients and methods

Clinical data

To incorporate the case data from the two sites in Chongqing, China, we conducted a retrospective cohort analysis. Retrospective data collection was conducted for patients with rectal cancer treated at the Chongqing University Cancer Hospital and the First Affiliated Hospital of Chongqing Medical University between January 2013 and December 2021. The inclusion criteria were as follows: 1) biopsy-confirmed adenocarcinoma of the rectum, 2) patient consent to LAPR, and 3) radical resection. The exclusion criteria were as follows: 1) history of other malignant tumors, multiple primary CRCs, or pathological diagnosis of non-adenocarcinoma; 2) anal preservation; 3) combined organ resection; 4) non-laparoscopic surgery or conversion to open administration; 5) history of radiotherapy for conditions other than rectal cancer; 6) no radical operation or clinical stage IV (including inguinal lymph node metastasis or lateral lymph node metastasis); and 7) unknown clinical information or loss to follow-up.

According to the above criteria, a total of 619 individuals with LAPR were identified, but 139 patients were excluded because of insufficient clinical information or loss to follow-up. Finally, 473 cases were included. Among them, 165 cases were enrolled at the Chongqing University Cancer Hospital, and 308 cases were enrolled at the First Affiliated Hospital of Chongqing Medical University.

According to the inclusion and exclusion criteria, participants were divided into a perineal incision infected group and a non-infected group according to the presence of perineal incision infection. All patients were operated on by experienced senior physicians.

Preoperative therapeutic schedule

Every patient who was included underwent a thorough preoperative assessment, which included a pelvic MRI, colonoscopy, enhanced CT of the chest and abdomen, and tumor markers. Preoperative neoadjuvant chemoradiotherapy is recommended for patients with preoperative T stage T3 or T4, N stage N1 or N2, positive perioperative margin [circumferential resection margin (CRM)], or positive extramural vascular invasion (EMVI). The neoadjuvant chemoradiotherapy regimen comprised conventional long-term radiotherapy with a single dose of 1.8–2.0 Gy administered a total of 25–28 times. For 8–12 weeks of preoperative chemotherapy, the regimen included fluorouracil or capecitabine alone or a combination of CapeOX (capecitabine and oxaliplatin) or FOLFOX (fluorouracil and oxaliplatin). At 8–12 weeks after the end of radiotherapy, surgical treatment was performed after evaluation of the specific condition of the patient's tumor.

Operation

For abdominal surgery, the rectum was separated from the levator ani plane according to the total mesorectal excision (TME) principle, and the sigmoid colon was dissected 10 cm above the tumor. Extraperitoneal stoma or transrectus abdominis stoma were used for stoma. For perineal surgery, the patient was still in the lithotomy position. The anus was closed with a double purse-string suture, and the skin on both sides of the perineum and back and the adipose tissue of the ischial anal canal were dissected according to the standard APR scope. The adipose tissue was first separated from the sacrococcygeal region in the abdominal cavity, and then the adipose tissue of the ischial anal canal was gradually separated and incised from both sides. The posterior margin of the superficial transperineum muscle was incised in the front, and the anterior part of the rectum was connected to remove the specimen. After the wound was completely hemostatic, the pelvic and abdominal wounds were washed with warm water, the perineum was redisinfected and covered with towels, the presacral drainage tube and subcutaneous negative pressure drainage ball were indwelled, and the subcutaneous tissue and skin were sutured with a tension-reducing needle at intervals and full thickness.

Postoperative adjuvant treatment

Pharmacy medication records were consulted, and patient in-hospital data or telephone follow-up data were collected. Postoperative adjuvant chemotherapy included fluorouracil or capecitabine alone, CapeOX, or FOLFOX.

Follow-up

All patients underwent follow-up evaluations in the outpatient clinic 3–6 months postoperatively. Every 3 months, tests for tumor markers, including at least blood levels of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), were performed. Enhanced CT scans of the abdomen and pelvis were conducted once every 6 months, and a colonoscopy was performed once per year. Patients who did not return to the hospital for reexamination were followed up by telephone according to a schedule, and the survival status, symptoms of discomfort, and local examination results were recorded. Study follow-up continued until 1 July 2022.

Observation indicators and evaluation criteria

General data, the perioperative period, and tumor prognosis between groups were analyzed. The infection rate, recurrence rate, and survival rate were compared between centers. This study mainly compared the prognosis of tumors between groups, including local recurrence and distant metastasis. Local recurrence refers to local tumors in the pelvic and perineal regions, as confirmed by imaging or reoperation pathology. The distant recurrence rate was defined as metastasis/recurrence of non-local recurrence sites, as confirmed by imaging or reoperation pathology.

Statistical analysis

SPSS 23.0 software was used for statistical evaluation. Quantitative information was presented as Xs, and t-tests were used to compare groups. In this study, [n (%)] was used to express categorical data. For group comparison and univariate analysis, we used chi-square or Fisher exact test. In the analysis of the survival curve, multivariate logistic analysis was applied to characterize OS and DFS.

Results

Basic data analysis

The total infection incidence for perineal wounds was 33.62%; there were 159 instances of infection and 314 cases without infection. No significant differences were observed in age, BMI (weight/height^2), comorbidities, and preoperative treatments between groups ($P > 0.005$, Table 1). The percentage of men in the experimental group was much

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TABLE 1 Patient characteristics.

	Infection group (n=159)	Non-infection group (n=314)	P
Gender			0.030
Male	87 (54.72%)	204 (64.96%)	
Female	72 (45.28%)	110 (35.03%)	
Age (years)	59.67±13.089	60.58 ± 10.937	0.452
Height (cm)	160.82 ± 9.238	161.47 ± 7.717	0.448
Weight (kg)	59.81 ± 10.935	59.19 ± 9.995	0.537
BMI (kg/m^2)	23.07 ± 3.372	22.64 ± 3.051	0.159
History of smoking			0.455
Yes	37 (23.27%)	83 (26.43%)	
No	122 (76.73%)	231 (73.57%)	
History of alcohol consumption			0.761
Yes	40 (25.17%)	75 (23.89%)	
No	119 (74.85%)	239 (76.11%)	
Diabetes mellitus			0.753
Normality	14 (8.81%)	25 (7.96%)	
Abnormality	145 (91.19%)	289 (92.04%)	
Hypertension			0.093
Normality	33 (20.75%)	46 (14.65%)	
Abnormality	126 (79.24%)	268 (85.35%)	
Neoadjuvant therapy			0.543
Yes	24 (15.09%)	41 (13.06%)	
No	135 (84.91%)	273 (86.94%)	

greater than that in the control group (P < 0.005). The preoperative neoadjuvant therapy was long-term radiotherapy, followed by 6–12 weeks of neoadjuvant chemotherapy, followed by radical surgery.

Operation and pathological stage

No significant differences were observed in the operation time, blood loss, distance between tumor and anus, tumor size, T stage, N stage, tumor stage, and number of positive lymph nodes between groups (P > 0.05, Table 2). The average length of hospital stay in the infection group was significantly longer than that in the non-infection group (P < 0.05). The distance was the shortest path between the tumor's bottom margin and the anus. Tumor size referred to the longest tumor diameter. Six patients achieved a pathological complete response (PCR) after preoperative treatment.

Adjuvant therapy

Postoperative adjuvant medication was administered to 192 patients in the non-infection group and 102 patients in the infection group. The initial chemotherapy session lasted substantially longer in the experimental group than that in the control group (P < 0.05), whereas the number of postoperative adjuvant chemotherapy showed no difference (P > 0.05), as shown in Table 3.

Follow-up

In the follow-up, in comparison to those in the non-infection group, the infection group's rates of recurrence and metastasis, local recurrence, and death were all considerably higher (P < 0.005, Table 4). In the infection group, 77 cases had recurrence and metastasis, whereas in the non-infection group, 68 cases had recurrence and metastasis. In the first recurrence and metastasis, the local recurrence rate of the infected group was much higher than that of the non-infection group (77.92% vs. 48.53%). DFS (P = 0.000) and OS (P = 0.005) significantly decreased in the infection group (Figure 1).

Comparison between centers

The infection rate, postoperative average length of hospital stay, metastasis rate, and mortality rate did not significantly differ between centers (Table 5). The overall infection rate in the two centers was 42.63%, the recurrence rate of metastasis was 30.65%, and the mortality rate was 20.72%.

Multiple-factor analysis

Univariate analysis of postoperative metastasis and recurrence of rectal cancer indicated that body weight, BMI, operation time, number of positive lymph nodes, N stage, tumor

TABLE 2 Surgical conditions and postoperative pathological features.

	Infection group (n=159)	Non-infection group (n=314)	P
Operating time (min)	265.28 ± 85.769	254.80 ± 77.805	0.182
Intraoperative bleeding (ml)	129.59 ± 112.902	142.52 ± 186.722	0.423
Distance (cm)	3.09 ± 1.499	3.18 ± 1.297	0.516
Tumor size (cm)	4.40 ± 1.902	4.13 ± 1.579	0.101
T stage			0.619
T0	2 (1.26%)	4 (1.27%)	
T1	8 (5.03%)	11 (3.50%)	
T2	47 (29.56%)	81 (25.79%)	
T3	55 (34.59%)	105 (33.44%)	
T4	47 (29.56%)	113 (35.99%)	
N stage			0.248
N0	103 (64.78%)	191 (60.83%)	
N1	29 (18.24%)	78 (24.84%)	
N2	27 (16.98%)	45 (14.33%)	
Pathological stage			0.974
0	2 (1.26%)	4 (1.27%)	
I	40 (25.16%)	74 (23.57%)	
II	59 (37.11%)	120 (38.22%)	
III	58 (36.48%)	116 (36.94%)	
Positive lymph node (n)	1.81 ± 3.735	1.39 ± 2.761	0.204
Differentiation degree			0.697
Poorly	5 (3.14%)	15 (4.78%)	
Moderately	150 (94.34%)	292 (92.99%)	
Well	4 (2.52%)	7 (2.23%)	
Postoperative hospital stay (days)	19.31 ± 14.148	12.62 ± 5.336	0.000

stage, infection, and postoperative hospital stay were statistically significant. After adjustment for the above factors, the risk of recurrence and metastasis was increased in patients with vaginal wound infection (odds ratio (OR) = 3.526, 95% CI: 2.228–5.578, P = 0.000). Univariate analysis of death due to rectal cancer indicated that the operation time, number of positive lymph nodes, N stage, tumor stage, infection, and postoperative hospital stay were statistically significant. After adjustment for the above factors in the logistic regression model, the perineal wound infection group had an increased risk of death (OR = 1.815, 95% CI: 1.107–2.976, P = 0.018).

Discussion

CRC has a high incidence and mortality. In 2020, globally, more than 1.9 million new cases of CRC and 935,000 deaths have been estimated to result from CRC, accounting for approximately one-tenth of all cancer cases and fatalities (10). However, the incidence and mortality of CRC are almost twice as high in men than those in women (9). In the data included in this study, the incidence was approximately 1.60 times higher in men than that in women, in line with the tumor distribution. The overall death rate for individuals with rectal cancer in this study was 20.72%, a finding consistent with the high mortality rate reported in the literature.

CRC is treated mainly with surgery. In China, the incidence of rectal cancer accounts for approximately 50% of CRCs, whereas lower rectal cancer accounts for 60%–70% of all CRCs. Postoperative complications of rectal cancer are significantly higher than those of colon cancer (11), with rates reaching 40% (12), according to the literature. However, APR has higher postoperative complications; most data have indicated an incidence of perineal complications of 10.1%–45% (9, 13–15). After preoperative neoadjuvant chemo radiotherapy, the incidence of perineal complications can even reach 60%–70% (9, 16). Wound infection is the main complication in the perineal area after APR. The perineal

TABLE 3 Time and frequency of postoperative chemotherapy.

	Infection group (n=102)	Non-infection group (n=192)	P
Time of first chemotherapy (days)	43.82 ± 16.337	29.91 ± 11.012	0.000
Frequency	5.11 ± 1.794	5.41 ± 1.682	0.368

TABLE 4 Prognosis.

	Infection group (n=159)	Non-infection group (n=314)	P
Recurrence/Metastasis			0.000
Yes	77 (48.43%)	68 (21.66%)	
No	82 (51.57%)	246 (78.34%)	
Position			0.001
Local	37 (48.05%)	19 (27.94%)	
Local and distant	23 (29.87%)	14 (20.59%)	
Distant	17 (22.08%)	35 (51.47%)	
Death			0.004
Yes	45 (28.30%)	53 (16.88%)	
No	114 (71.70%)	261 (83.12%)	

wound infection rate was found to be 32.73%, in agreement with the literature, possibly because the sacral cavity forms a large wound area after rectum resection, thus resulting in fluid accumulation and pelvic abscess. In addition, the operation time of LAPR is longer, thus potentially increasing the risk of postoperative infection. Wound infection increases medical expenses, prolongs hospital stay, and decreases patient quality of life (17). In this study, in comparison to that in the non-infection group, the average postoperative hospital stay in the infected group was much longer (19.31 days vs. 12.62 days).

After CRC surgery, SSI can decrease the DFS after radical surgery (6, 7) but has not been demonstrated to be associated with OS. Anastomotic leakage after rectal surgery promotes local recurrence and decreases DFS and OS according to several studies (18–22). However, anastomotic leakage has been found to increase local recurrence without affecting OS or DFS (23). Thus, this conclusion is controversial at present. In gastric cancer, SSI has been reported to decrease OS after radical surgery (24), and anastomotic leakage has been found to decrease OS after gastric cancer surgery according to several studies (25, 26). However, this conclusion is still debatable. Anastomotic leakage after treatment for stomach cancer, according to some research, has no effect on prognosis (27). However, no study has examined the relationship between wound infection and prognosis after gastric CRC surgery. This study showed that perineal wound infection increased the local tumor recurrence rate and decreased the OS and DFS. Simultaneously, after rectal cancer surgery, perineal wound infection is a separate risk factor for both DFS and OS.

At present, the mechanism of LAPR wound infection and poor tumor prognosis is unclear. Inflammation may be activated by wound infection in the perineal region. However, inflammatory cells produce tumor necrosis factor-α, transforming growth factor-β, interleukin-6 (IL-6), and other cytokines, which regulate the transcription factor NF-κB and the signal transducer and activator of transcription-3 (STAT3) pathways, and promote tumor cell metastasis (28–30). Another research has shown that inflammatory cells cause overexpression of vascular endothelial growth factor (VEGF) and IL-6 (31). The most potent angiogenic cytokine is VEGF, and angiogenesis plays a major role in tumor spread and recurrence (32). Shorter DFS and OS are associated with elevated blood VEGF levels in patients

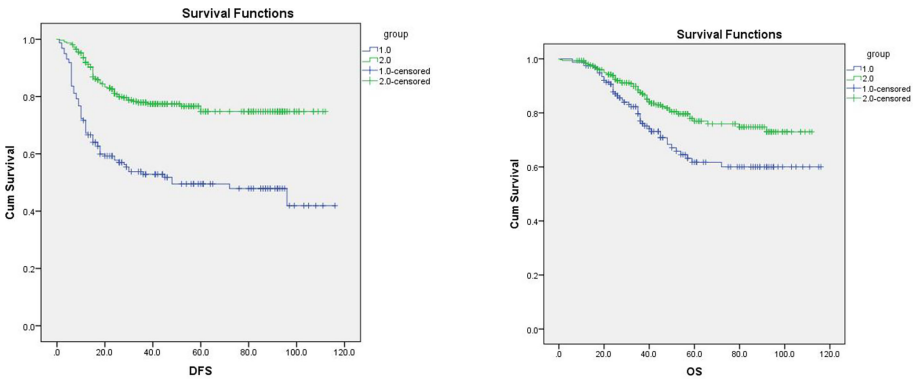

FIGURE 1
Overall survival (OS) and PFS of the two groups. Note: Group 1 is the infection group, and group 2 is the non-infection group. The longest follow-up was 120 months, in which changes in disease-free survival (DFS) and overall survival (OS) were significant (P < 0.05).

TABLE 5 Comparative analysis of the two centers.

	First Affiliated Hospital (n=308)	Cancer Hospital (n=165)	P
Infection			0.765
Yes	105 (34.09%)	54 (32.73%)	
No	203 (65.91%)	111 (67.27%)	
Postoperative hospital stay (days)			0.352
	14.56 ± 11.126	15.44 ± 6.620	
Recurrence/Metastasis			0.903
Yes	95 (30.84%)	50 (30.30%)	
No	213 (69.16%)	115 (69.70%)	
Death			0.141
Yes	70 (22.73%)	28 (16.97%)	
No	238 (77.27%)	137 (83.03%)	

with CRC (33, 34). In this study, wound infection in the perineal area of LAPR resulted in the activation of inflammatory cells, which might have led to the systemic inflammatory response syndrome, thereby increasing the risk of postoperative tumor spread. Furthermore, in CRC, after resection, cancer cells that are still present in the large intestine's mucosa and intestinal lumen may peel off and become implanted in the surrounding area (35). In addition, inflammation in the abdomen can help cancer cells adhere together, move around, and invade other tissues, whereas the wound infection in the perineal area after LAPR is mainly confined to the pelvic cavity, thus resulting in local adhesion, tumor cell invasion, and migration. Consequently, in comparison to the non-infection group, the infection group's local recurrence rate was significantly greater (77.92% vs. 48.53%). Finally, postoperative adjuvant chemotherapy may prolong OS and decrease postoperative recurrence in stage II/III rectal cancer (36). According to National Comprehensive Cancer Network (NCCN) guidelines, postoperative adjuvant chemotherapy should be performed within 3 weeks and generally not more than 8 weeks. According to a meta-analysis, extended adjuvant chemotherapy beyond 8 weeks dramatically shortens DFS and OS (37, 38). In our study, although the mean time to the first postoperative chemotherapy in the infected group did not exceed 8 weeks, it was much longer than that in the non-infection group. This finding might indicate one factor contributing to the infected group's elevated risk of local recurrence.

Studies have shown that minimally invasive techniques can reduce SSI (39); this conclusion has also been confirmed in CRC (40, 41) and through urology (42). Moreover, LAPR combined with pelvic peritoneal closure can decrease the infection rate after APR (43). The postoperative infection incidence of rectal cancer may be decreased by oral antibiotics and mechanical bowel preparation (44). Preoperative neoadjuvant chemo radiotherapy, the main treatment for locally advanced rectal cancer, has been found to decrease the tumor stage and thus improve the R0 removal rate of tumors, and this conclusion has been confirmed with total neoadjuvant therapy (TNT) (45–47). However, neoadjuvant chemoradiotherapy has been the most frequently documented risk factor for SSI after APR in recent years (48–50). Unfortunately, no available evidence suggests that preoperative neoadjuvant treatment increases the incidence of LAPR wound infection. In this study, only 13.74% of patients received preoperative radiotherapy. Therefore, in LAPR, preoperative mechanical bowel preparation, oral antibiotics, intraoperative aseptic procedures, and closure of the basin peritoneum may limit the wound infection rate and thus improve tumor prognosis.

This study's primary limitation was its retrospective methodology. However, we collected data continuously from two institutional databases to avoid data selection bias to some extent. However, this conclusion still must be confirmed in a prospective multicenter large-sample study.

Conclusions

Wound infection after LAPR increased the postoperative hospital stay, delayed the time of postoperative first adjuvant chemotherapy, increased the postoperative tumor recurrence and metastasis, and decreased the survival time in patients. Therefore, limiting the wound infection rate of LAPR is expected to shorten the postoperative hospital stay, decrease the time of the first adjuvant chemotherapy, and improve the DFS, OS, and tumor prognosis. Intensive postoperative adjuvant therapy may be needed in patients with postoperative infection.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

WH made important contributions to the research conception and design, as well as to the analysis and

interpretation. WH, Y-hQ, and GT participated in the data collection. WH wrote the manuscript. HS and Z-qW supervised and edited the manuscript. WH is the first author, and HS is the corresponding author. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Alberto Puccini,
Ospedale Policlinico San Martino IRCCS, Italy

REVIEWED BY
Lin Wu,
Hunan Cancer Hospital, Xiangya School of Medicine, Central South University, China
Gabriele Multhoff,
Technical University of Munich, Germany

*CORRESPONDENCE
Jinliang Wang
wangjinliang301@126.com
Fan Zhang
zhangfan@301hospital.com.cn
Yi Hu
huyi301zlxb@sina.com

†These authors have contributed equally to this work

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Effectiveness and safety of anti-PD-1 monotherapy or combination therapy in Chinese advanced gastric cancer: A real-world study

Tao Li[1,2,3†], Tingting Liu[1,4†], Lei Zhao[5†], Lu Liu[1,6], Xuan Zheng[1,2,3], Jinliang Wang[1,7*], Fan Zhang[1,2,3*] and Yi Hu[1,2,3*]

[1]Graduate School, Medical School of Chinese People's Liberation Army (PLA), Beijing, China, [2]Department of Oncology, The First Medical Center, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China, [3]Chinese People's Liberation Army (PLA) Key Laboratory of Oncology, Key Laboratory for Tumor Targeting Therapy and Antibody Drugs, Ministry of Education, Beijing, China, [4]Department of Pulmonary and Critical Care Medicine, the Second Medical Center, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China, [5]Institute of Translational Medicine, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China, [6]Department of Nutrition, The First Medical Center, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China, [7]Department of Oncology, The Fifth Medical Center, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China

Purpose: Gastric cancer (GC) is one of the most frequently diagnosed cancers and one of the leading causes of cancer deaths worldwide, especially in eastern Asia and China. Anti-PD-1 immune checkpoint inhibitors, Pembrolizumab and Nivolumab, have been approved for the treatment of locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC). Our study evaluated the effectiveness and safety of anti-PD-1-based treatment (monotherapy or combination therapy) in Chinese patients with advanced or metastatic GC/GEJCs in a real-world setting.

Methods: A retrospective cohort study was conducted, and 54 patients from May 31, 2015, to May 31, 2021, were included in our analysis, including 19 patients treated with anti-PD-1 monotherapy and 35 patients treated with anti-PD-1 combination therapy. Demographic and clinical information were evaluated. Clinical response, survival outcomes, and safety profile were measured and analyzed.

Results: Overall, the median overall survival (mOS) was 11.10 months (95% CI, 7.05–15.15), and the median progression-free survival (mPFS) was 3.93 months (95% CI, 2.47–5.39). Of the patients, 16.7% achieved a clinical response, and 72.2% achieved disease control. Prolonged overall survival (OS) and progression-free survival (PFS) and increased clinical response were observed in the combination group compared with the monotherapy group, although statistical significance was not reached. In subgroups with live metastases or elevated baseline neutrophil-to-lymphocyte ratio (NLR) levels, combination therapy outperformed anti-PD-1 alone in survival outcomes. Patients treated with anti-PD-1 monotherapy (n = 5, 26.3%) had fewer treatment-related

adverse events (TRAEs) than those in the combination group (n = 22, 62.9%). There were also fewer patients with TRAEs of grades 3–5 with monotherapy (n = 2, 10.5%) than with combination therapy (n = 7, 20.0%). Pneumonitis in three patients was the only potential immune-related adverse event reported.

Conclusions: Anti-PD-1-based monotherapy and combination therapy showed favorable survival outcomes and manageable safety profiles in advanced or metastatic GC/GEJCs. In clinical treatment, immunotherapy should be an indispensable choice in the treatment strategy for GC/GEJC. Patients with a heavy tumor burden and more metastatic sites might benefit more from combination therapy. Elderly patients and patients with more treatment lines or high Eastern Cooperative Oncology Group (ECOG) performance scores might be more suitable for immune monotherapy, and some clinical benefits have been observed.

KEYWORDS

anti-PD-1, gastric cancer, real-word study, Chinese, efficacy and safety analyses

1 Introduction

Gastric cancer (GC) is one of the most frequently diagnosed cancers and one of the leading causes of cancer deaths worldwide (1). It is more prevalent in eastern Asia and China. The estimated incidence and mortality of GC in 2015 were 679,100 and 498,000, respectively, ranking as the second most common cancer (2, 3). Most patients are diagnosed at an advanced stage, with a 5-year survival rate of only 33% (4). Currently, the first-line treatment for advanced GC patients is primarily platinum plus fluoropyrimidine, or trastuzumab in combination with it, for HER2-overexpressing tumors (5, 6). Preferred treatment modalities for second-line or beyond include ramucirumab plus paclitaxel or monotherapy of docetaxel, paclitaxel, irinotecan, or ramucirumab (5).

In recent years, immunotherapy has been a revolutionary treatment strategy for advanced cancers. Immune checkpoint blockades (ICBs), including antibodies to Programmed Death Receptor 1 (PD-1) or its ligand (PD-L1), are now standard therapies for a range of solid tumors as approved by the Food and Drug Administration (FDA) (7). Several clinical trials have shown that some GC patients could benefit from anti-PD-1/PD-L1 antibody therapy, indicating that ICBs are a potential treatment option for GC. For ICBs' monotherapy as third-line, pembrolizumab (a humanized anti-PD-1 IgG4 monoclonal antibody) was approved by the FDA for the treatment of locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC) patients with PD-L1 positive tumors (Combined Positive Score (CPS) ≥1). This is based on the data of KEYNOTE-059, a single-arm study (8). In ATTRACTION-2, a phase III clinical trial comparing nivolumab with a placebo in Asian patients who were heavily pretreated, nivolumab (a humanized anti-PD-1 IgG4 monoclonal antibody) led to improved overall survival (OS) and progression-free survival (PFS) and was, in general, well tolerated (9). However, in another phase III clinical trial conducted on a global scale (JAVELIN gastric 300), avelumab (a humanized anti-PD-L1 IgG1 monoclonal antibody) did not improve OS or PFS compared with chemotherapy in the total population (including 25.4% Asian patients) as a third-line treatment (10). For first- or second-line treatment, only three single-arm studies showed a 7%–22% objective response rate (ORR) from ICB monotherapy (11–13), and two phase III trials reported no significant clinical benefit from pembrolizumab monotherapy compared with chemotherapy (14, 15). Because of the modest benefit of ICB monotherapy, co-administration with another therapeutic agent provides a potential solution to enhance treatment effectiveness. However, in KEYNOTE-062, the only phase III study investigating pembrolizumab plus chemotherapy as first-line treatment of advanced GC/GEJCs, the arm given pembrolizumab plus chemotherapy did not exhibit significantly prolonged OS than those taking chemotherapy alone (15). Several phase I-II studies

Abbreviations: AE, Adverse events; DCR, Disease control rate; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; GC, Gastric cancer; HR, Hazard Ratio; ICB, Immune checkpoint blockades; NLR, Neutrophil-to-lymphocyte ratio; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PLA, People's Liberation Army; PLR, Platelet-to-lymphocyte ratio; SPSS, SPSS statistical; TRAE, Treatment-related adverse events

preliminarily showed that ICBs combined with chemotherapy, targeted, or antiangiogenic agents presented improved ORR (16–18). Most of the studies above were conducted on Caucasian patients, while little was known about how Asian GC/GEJCs patients, either treatment-naïve or previously treated, would respond to ICBs therapy. This represents an unmet medical need since Asians are known to be heavily burdened with GC/GEJCs. Moreover, the populations in the clinical trials described above are usually highly selected. It remains inconclusive whether patients with an Eastern Cooperative Oncology Group (ECOG) performance score 1, patients with brain metastases, or patients over 70 years old could benefit from ICBs' treatment since they are usually excluded from interventional clinical trials. To explore whether ICBs could bring clinical benefit to Asian GC patients, especially in China, we conducted a real-world study to examine the safety and anti-tumor effectiveness of anti-PD-1 monotherapy and combination therapy in advanced GC patients. To our knowledge, it was one of the first real-world clinical studies of immunotherapy for GC/GEJC in China. Through this study, it was hoped that real-world studies could play a complementary role in clinical trials and provide more evidence-based medical support for immunotherapy for GC/GEJC in Asia, especially in China.

2 Materials and methods

2.1 Study design and participants

This study conducted a retrospective analysis to evaluate the effectiveness and safety profile of anti-PD-1 treatment in a real-world setting. Consecutive GC/GEJCs patients treated at the Department of Oncology, Chinese People's Liberation Army (PLA) General Hospital from May 31, 2015, to May 31, 2021, were reviewed and screened. Inclusion criteria were: 1) pathologically confirmed GC/GEJCs; 2) advanced or metastatic disease or recurrence after curative surgery; and 3) administration of nivolumab or pembrolizumab as monotherapy or combination therapy. The ethics committee of PLA General Hospital approved this study according to the ethical standards of the Declaration of Helsinki and its subsequent amendments (Ethical approval number: S2020-284-01).

Clinicopathological characteristics were reviewed and collected. Two physicians independently extracted and recorded demographic and clinical information, followed by confirmation by a third physician in case of inconsistency. Data were collected from the following sources: 1) Chinese PLA General Hospital inpatient and outpatient records, including doctors' notes, radiographic reports, and biopsy results; 2) patient or family interviews. Complete blood cell counts of eligible patients, covering neutrophils, lymphocytes, thrombocytes, and erythrocytes, were also collected. NLR was defined as the absolute neutrophil count divided by the entire lymphocyte count in peripheral blood, collected before the initiation of anti-PD-1 treatment. The platelet-to-lymphocyte ratio (PLR) was defined as the absolute thrombocyte count divided by the absolute lymphocyte count. Median NLR and PLR were adopted as cutoffs in our analysis.

2.2 Study objectives

The primary endpoint was OS, defined as the time from the first dose of anti-PD-1 to death from any cause. Secondary endpoints included PFS (defined as the time from treatment initiation to the first documented disease progression or death), ORR (defined as the proportion of patients with confirmed complete response or partial response), and disease control rate (DCR), which was defined as the proportion of patients with confirmed complete response, partial response, or stable disease, duration of response, and the maximum percentage change from baseline for the sum of diameters of target lesions. All endpoints were evaluated according to RECIST (version 1.1) guidelines (19). Follow-up imaging reports were reviewed by two radiologists independently. The director of the imaging center further verified any discrepancies. Data for patients without disease progression or death events were censored at the time of the last follow-up. Adverse events (AE) were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (20). Treatment-related adverse events (TRAEs) and immune-related AEs were graded and recorded. All patients were followed up until December 2021, or death.

2.3 Ethics approval and consent to participate

All participants in this study signed informed consent forms. The ethics committee of the PLA General Hospital approved this study according to the ethical standards of the Declaration of Helsinki and its subsequent amendments (Ethical approval number: S2020-284-01).

2.4 Statistical analysis

Categorical characteristics and objective response were compared between treatment groups with the chi-square test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Kaplan-Meier survival analysis was used to assess OS and PFS, and the log-rank test was used to compare groups. The Hazard Ratio (HR) was estimated using the Cox proportional hazard model. In the multivariable Cox regression model, variables with a P-value <0.10 in the univariable Cox regression or acting as clinically relevant

factors were adjusted. All *P*-values are two-tailed, and a *P*-value <0.05 was considered statistically significant. The SPSS statistical package (SPSS 20, SPSS, Chicago, IL, USA) was used for all statistical analyses.

3 Results

3.1 Patients' characteristics and treatment

Fifty-four patients received anti-PD-1-based therapy during their course of disease and were identified and included in our analysis, including 19 patients treated with anti-PD-1 monotherapy and 35 patients treated with anti-PD-1 combined with chemotherapy (XELOX, SOX, and mFOLFOX6) targeted therapy or anti-CTLA-4 (a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen-4). Patients' clinicopathological characteristics are summarized in Table 1. The median age of the recruited patients was 58 years in the monotherapy group and 59 years in the combination therapy group, where 2 (10.5%) and 9 (25.7%) patients received immunotherapy at the age of over 65 in the two groups, respectively. In the two groups, 11 (57.9%) and seven patients (20.0%) had an ECOG performance score of 2-4, respectively. Fewer patients in the monotherapy group received anti-PD-1 as first-line treatment than in the combination group (5.3% vs. 37.1%, $P = 0.01$), while more patients in the monotherapy groups were treated with anti-PD-1 as 4th line or later therapy (36.8% vs. 11.4%, $P = 0.04$), respectively. Due to the long period, people initially did not realize that PD-L1 status was vital for immunotherapy when the drug was marketed, so only a small number of patients completed the test. Only 5/19 and 8/35 patients from monotherapy and combination therapy completed the PD-L1 test respectively (Table 1).

3.2 Treatment outcome

As of the data cut-off date of May 31, 2021, the median follow-up was 9.40 months, ranging from 0.80 to 43.80 months. 44 (81.5%) progression events and 37 (68.5%) deaths occurred during the follow-up period. In the overall cohort, the mOS was 11.10 months (95% CI, 7.05–15.15), and the mPFS was 3.93 months (95% CI, 2.47–5.39). Prolonged mOS was observed in the patients receiving combination therapy (11.10 months; 95% CI, 7.18–15.03), and that was over those taking anti-PD-1 alone (5.40 months; 95% CI, 2.64–8.17). However, the difference in OS between the two groups was not statistically significant, possibly due to the small sample size (HR = 0.70, 95% CI, 0.36–1.35, $P = 0.29$) (Figure 1). Likewise, the mPFS of the combination group at 4.07 months (95% CI, 1.83–6.03) was non-significantly longer than that of the monotherapy group at 2.93 months (95% CI, 0.85–5.01) (HR = 0.69, 95% CI, 0.37–1.26, $P = 0.22$) (Figure 2).

In the overall population, for patients who received anti-PD-1-based therapy as first- or second-line treatment, the mOS and mPFS were, respectively, 11.10 months (95% CI, 6.36–15.85) and 3.43 months (95% CI, 2.20–4.66). In patients treated with anti-PD-1-based therapy as the third-line or beyond, the mOS and mPFS were 9.13 months (95% CI, 2.22–16.04) and 4.20 months (95% CI, 1.60–6.80), respectively. There was no statistical difference between the monotherapy and combination groups regarding OS or PFS upon stratification by treatment lines (Supplementary Figures 1–4). The duration of treatment and outcomes for each patient were specified in Figure 3.

Response rates for the overall population, the monotherapy group, and the combination arm were summarized in Table 2. ORR and DCR were 16.7% (95% CI, 6.4–26.9%) and 72.2% (95% CI, 59.9–84.6%) of the overall cohort, respectively. ORR tended to be higher in the combination group (20.0%, 95% CI, 8.4–36.9%) than in the monotherapy group (10.5%, 95% CI, 1.9–29.6%), but the difference was not statistically significant ($P = 0.47$) with the limited sample size. DCR was 63.2% and 77.1% in the monotherapy and combination groups, respectively ($P = 0.35$). Concerning the best overall responses, 36.8% (7/19) of the patients given monotherapy and 40.0% (14/35) of the patients on combination treatment achieved a decrease from baseline in the sum of their target lesions (Figure 4).

We also did subgroup analysis to compare the survival outcomes of monotherapy and combination therapy according to different stratifications (Table 3). In patients with liver metastases or elevated NLR levels (NLR above the median), anti-PD-1 administered in conjunction with other medications led to a more favorable mOS compared to those on monotherapy. (The HR in the subgroup with liver metastases was 0.33, 95% CI, 0.11–1.00, $P = 0.05$; HR in the subgroup with elevated NLR was 0.38, 95% CI, 0.14–1.00).

Of the five patients who accepted anti-PD-1 combined with apatinib, a small molecular anti-angiogenic agent, in the combination group, they all achieved a durable, stable disease, ranging from 4.20 to 9.37 months, although no objective response was observed.

3.3 Association between clinicopathological characteristics and survival outcomes

In univariate analyses with the Cox regression model, ECOG 0–1 was associated with better OS outcome (HR = 0.28, 95% CI, 0.11–0.56) (Supplementary Table 1). Patients with ascites and elevated NLR or PLR were at higher risk of death (HR for ascites was 3.27, 95% CI, 1.61–6.65, $P = 0.001$; HR for elevated NLR was 2.19, 95% CI, 1.18–4.05, $P = 0.01$; and HR for elevated PLR was 2.49, 95% CI, 1.33–4.65, $P = 0.004$). In light of the results from

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TABLE 1 Baseline demographic and clinical characteristics of GC/GEJC patients.

	Univariate Cox model			Multivariate Cox model		
Characteristics	HR	95%CI	P value	HR	95%CI	P value
Gender	0.61	0.31-1.24	0.17			
Male vs female						
Age	1.12	0.49-2.57	0.79			
≥65 vs <65						
EOCG performance status	0.28	0.11-0.56	**<0.001**	0.19	0.09-0.40	**<0.001**
0-1 vs 2-4						
Primary tumor site	0.38	0.05-2.78	0.34			
Gastric vs Gastro-oesophageal junction						
TNM stage	0.35	0.08-1.45	0.15			
III vs IV						
Metastasis	2.34	0.55-9.89	0.25			
Yes vs No						
Organs with metastases	1.32	0.68-2.53	0.41			
≤2 vs >2						
Ascites	3.27	1.61-6.65	**0.001**	4.36	2.02-9.44	**<0.001**
Yes vs No						
Lymph node metastases	1.52	0.54-4.29	0.43			
Yes vs No						
Peritoneum metastases	1.29	0.66-2.52	0.46			
Yes vs No						
Liver	0.60	0.31-1.16	0.13			
Yes vs No						
Treatment regimen	0.69	0.36-1.33	0.26	1.02	0.46-2.28	0.97
Com vs mono						
Treatment lines	0.84	0.44-1.62	0.61			
1-2 vs >2						
Elevated LDH	1.37	0.57-3.31	0.48			
Yes vs No						
NLR	2.19	1.18-4.05	**0.01**	1.65	0.65-4.21	0.29
>median vs <median						
PLR	2.49	1.33-4.65	**0.004**	1.96	0.74-5.16	0.17
>median vs <median						
Adverse event	0.80	0.41-1.55	0.50			
Yes vs No						

ECOG, Eastern Cooperative Oncology Group.
LDH, lactate dehydrogenase.
NLR, neutrophil to lymphocyte ratio.
PLR, Platelet to lymphocyte ratio.
The meaning of the bold values was P value <0.05 and was considered statistically significant.

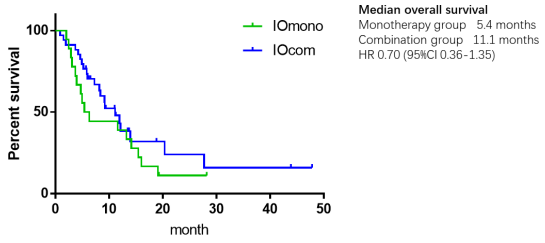

FIGURE 1
Kaplan-Meier plot of overall survival.

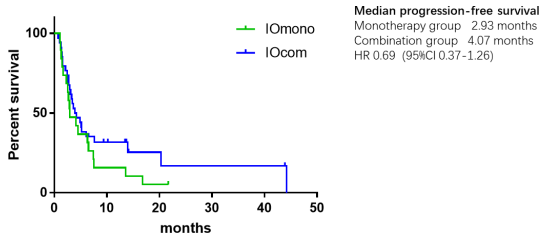

FIGURE 2
Kaplan-Meier plot of progression-free survival.

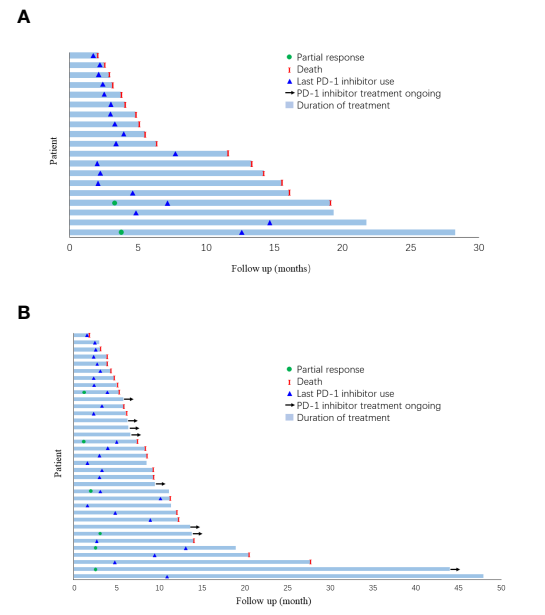

FIGURE 3
Duration of follow-up and outcome for each patient in **(A)** monotherapy group and; **(B)** combination group.

the univariate analyses, we selected the ECOG performance score, ascites, NLR, and PLR for multivariable analyses. ECOG performance score and ascites were independent risk factors associated with OS outcomes in patients treated with anti-PD-1-based therapy. NLR and PLR did not reach statistical significance in the multivariable analysis.

3.4 Safety and adverse events

TRAEs of any grade occurred in 27 patients (50%) in the overall cohort (Table 4). All-grade TRAEs observed in 5% or more of patients in the overall cohort included decreased neutrophil count, nausea, vomiting, increased alanine aminotransferase, and increased alkaline phosphatase levels. Patients treated with anti-PD-1 monotherapy (n = 5, 26.3%) had fewer TRAEs than those in the combination group (n = 22, 62.9%). There were also fewer patients with TRAEs of grades 3–5 with monotherapy (n = 2, 10.5%) than with combination therapy (n = 7, 20.0%). Grade 3 to 5 events were reported in nine patients (16.7%), including oral mucositis (n = 1, 5.3%) and gastric obstruction (n = 1, 5.3%) in the anti-PD-1 monotherapy group and decreased neutrophil count (n = 4, 11.4%), gastric perforation (n = 1, 2.9%), lung infection (n = 1, 2.9%), and pneumonitis (n = 1, 2.9%) in the combination group. Only one death was attributed to treatment in the combination group (one patient with gastric perforation). No deaths related to study treatment occurred in the monotherapy group. Pneumonitis was the only potentially immune-related adverse event reported in our cohort, which was observed in three patients (one with monotherapy and two with combination therapy).

4 Discussion

To our knowledge, this was one of the first real-world studies that evaluated the performance of an anti-PD-1-based treatment regimen in the Chinese GC/GEJC population. Anti-PD-1 monotherapy and combination therapy showed favorable survival outcomes and manageable safety profiles in advanced or metastatic GC/GEJCs. The mOS was 11.10 months (95% CI, 7.05–15.15), 5.40 months (95% CI, 2.64–8.17), and 11.1 months (95% CI, 7.17–15.03) in the overall population, the monotherapy group, and the combination group, respectively, while the mPFS was 3.93 months (95% CI, 2.47–5.39), 2.93 months (95% CI, 0.85–5.01), and 4.07 months (95% CI, 1.83–6.03). Prolonged OS and PFS were observed in the combination group compared with the monotherapy group, although statistical significance was not reached. Objective response was achieved in 16.7%, 10.5%, and 20.0% of patients in the overall population, monotherapy group, and combination group, respectively. In the overall cohort,

TABLE 2 Objective tumor response of GC/GEJC patients.

	Monotherapy (n=19)	Combination therapy (n=35)	P value
Gender			1.00
Male	11(57.9%)	21(60.0%)	
Female	8(42.1%)	14(40.4%)	
Age			0.29
Median (range), years	58(34–81)	59(24-86)	
<65	17(89.5%)	26(74.3%)	
≥65	2(10.5%)	9(25.7%)	
ECOG performance status			**0.01**
0	2(10.5%)	21(60.9%)	
1	6(31.6%)	7(20.0%)	
2	6(31.6%)	5(14.3%)	
3	4(21.1%)	2(5.7%)	
4	1(5.3%)	0	
TNM stage			0.61
III	2(10.5%)	2(5.71%)	
IV	17(89.5%)	33(94.3%)	
Tumor site			0.54
Gastric	19(100%)	32(91.4%)	
Gastro-oesophageal junction	0	3(8.6%)	
Organs with metastases			0.25
≤2	7(36.8%)	20(57.1%)	
>2	12(63.2%)	15(42.9%)	
Site of metastases			
Lymph node	18(94.7%)	29(82.9%)	1.00
Peritoneum	13(68.4%)	18(52.9%)	0.26
Liver	5(26.3%)	22(64.7%)	**0.02**
Bone	4(21.1%)	8(23.5%)	1.00
Lung	3(15.8%)	4(11.4%)	0.68
Adrenal	1(5.3%)	3(8.8%)	1.00
Previous anticancer therapies for locally advanced/metastatic disease			
0	1(5.3%)	13(37.1%)	**0.01**
1	7(36.8%)	14(40.0%)	1.00
2	4(21.1%)	4(11.4%)	0.43
≥3	7(36.8%)	4(11.4%)	**0.04**
Previous gastrectomy			**0.01**
Yes	15(78.9%)	7(20.0%)	

(Continued)

TABLE 2 Continued

	Monotherapy	Combination therapy	
	(n=19)	(n=35)	P value
No	4(21.1%)	28(80.0%)	
PD-L1			0.59
Positive	2(10.5%)	4(11.4%)	
Negative	3(20%)	4(11.4%)	
Unkown	14(69.5%)	27(77.1%)	
Combined use			
Combined with chemotherapy (XELOX/SOX/FOLFOX)		24(68.6%)	
Combined with target therapy		4(11.4%)	
Combined with chemotherapy and target therapy		5(14.3%)	
Combined with ipilimumab		2(5.7%)	

Data are number of patients (%) unless specified otherwise.
ECOG, Eastern Cooperative Oncology Group.
The meaning of the bold values was P value <0.05 and was considered statistically significant.

72.2% of the patients achieved tumor regression or disease control (95% CI, 59.9–84.6%). In patients treated with anti-PD-1/L1 monotherapy as a third-line treatment, the mOS and mPFS were reported to be 4.6–5.6 months and 1.4–2.0 months, respectively (8–10). Among the patients treated as third-line or beyond treatment in our cohort, the mOS was 6.3 months (95% CI, 0–18.43) and the mPFS was 4.13 months (95% CI, 0.86–7.40). In phase II clinical trial, anti-PD-1 as a first-line treatment showed mOS of 13.8 months (95% CI, 8.6–not evaluable) in the monotherapy cohort and 20.7 months (95% CI, 9.2–20.7) in the combination cohort (21). Of the 14 patients in our cohort who received an anti-PD-1-based regimen as a first-line treatment, their mOS was 11.10 months (95% CI, not evaluable). Among these 14 patients, 4 (28.6%) had an ECOG performance score >1. That might explain the relatively inferior survival outcome compared with the previous report. In a phase Ib/II clinical trial, 18 Chinese metastatic GC patients received anti-PD-1 plus chemotherapy as first-line treatment, and 58 received anti-PD-1 monotherapy as second-line treatment. In the former cohort, mOS was not reached and mPFS was 5.8 months, while in the latter cohort, mOS was 4.8 months and mPFS was 1.9 months (22). In our cohort, 13 patients received anti-PD-1-based combination therapy as first-line treatment, with a mOS not reached and a mPFS of 5.2 months. Of the 18 patients who progressed after at least one systematic chemotherapy and were treated with anti-PD-1 monotherapy, the mOS was 6.3 months (95% CI, 0–15.54) and the mPFS was 2.87 months (95% CI, 0–5.91). Overall, our study showed results comparable to previously published interventional studies.

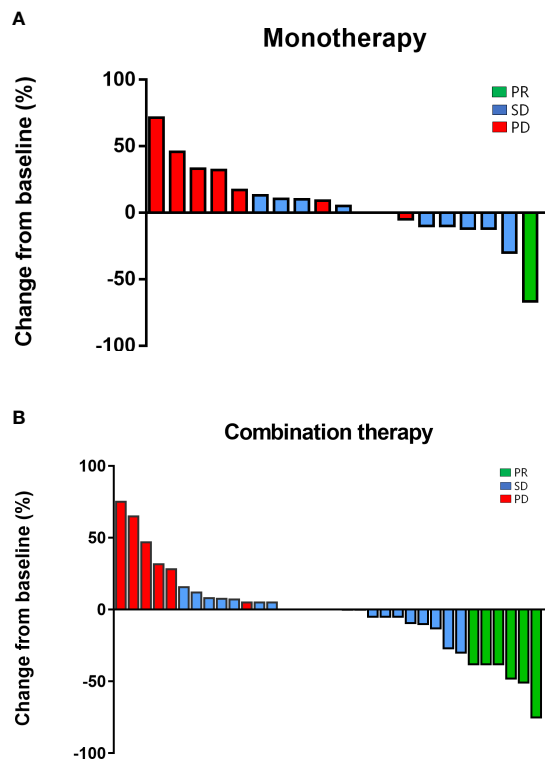

FIGURE 4
Regression of target lesions from baseline in each patient in **(A)** the monotherapy group and; **(B)** the combination group.

In a recent phase Ia/b clinical trial, 41 GC/GEJC patients whose disease progressed after one or two lines of systemic therapy were treated with pembrolizumab plus ramucirumab (an IgG1 VEGFR-2 monoclonal antibody). Of these patients, 21 (51%) achieved disease control, including 3 (7%) partial responses and 18 (44%), stable disease (23). In our cohort, five

TABLE 3 Subgroup analysis of overall survival by monotherapy and combination therapy.

	Overall population	Monotherapy	Combination therapy
Tumor response data	(n=54)	(n=19)	(n=35)
Complete response	0	0	0
Partial response	9(16.7%)	2(10.5%)	7(20.0%)
Stabe disease	30(55.6%)	10(52.6%)	20(57.1%)
Progressive disease	15(27.8%)	7(36.8%)	8(22.9%)
Objective response rate, 95%CI	9(16.7%; 6.4-26.9)	2(10.5%; 1.9-29.6)	7(20.0%; 8.4-36.9)
Disease control	39(72.2%; 59.9-84.6)	12(63.2%; 38.4-83.7)	26(74.3%; 56.7-87.5)
Data are n (%) or n (%; 95% CI).			

patients were given anti-PD-1 (three with pembrolizumab and two with nivolumab) combined with apatinib, and all five patients obtained clinical benefits with durable disease control. *De-novo* or acquired resistance to ICBs is complex and could be attributed to several factors, such as an immunosuppressive tumor microenvironment, a lack of PD-L1 expression, and T-cell exclusion (24–26). Anti-angiogenesis therapy could prevent immunotherapy resistance by increasing T-cell trafficking, migration across vascular endothelium, and infiltration into tumor tissue (27). Further studies with larger sample sizes are needed to verify the synergistic effects of anti-angiogenesis therapy with ICBs.

Patients recruited into randomized clinical trials are usually highly selected. Inclusion criteria typically include an ECOG performance score of <2 and no symptomatic brain metastases or other unfavorable physical conditions (28, 29). Randomized clinical trials provide an optimal way to evaluate the effectiveness and safety of a specific treatment. However, such studies are intrinsically less amenable to extrapolation. An ECOG performance score of >1 was previously reported as an independent risk factor for unfavorable survival upon treatment with ICBs in real-world studies (30, 31). In our cohort, of 18 patients with a baseline ECOG performance score of 2–4, only 5.6% (95% CI, 0–17.3%) obtained a clinical response. In contrast, for patients with a baseline ECOG of 0–1, the ORR was 22.2% (95% CI, 8.0–36.5%), and the mPFS was 5.20 months (95% CI, 2.03–8.37). Patients with ECOG 2–4 also had worse overall survival than those with ECOG 0–1 (median OS, 4.80 months vs. 13.23 months; HR = 3.54, 95% CI, 1.80–6.97). Consistent with previous studies, the ECOG performance score was validated as an independent OS risk factor (Table 4). Patients with brain metastases are usually excluded from randomized studies (9, 23). In our cohort, four patients had brain metastases at the onset of anti-PD-1 therapy; their mPFS was 1.30 months (95% CI, 1.05–1.56) and mOS was 8.37 months (95% CI, 0.98–15.75). In addition to the particular subpopulations mentioned above, there were nine patients in our study aged ≥70, among whom 10% responded to the treatment, and their mPFS and mOS were 3.07 months (95% CI, 2.66–3.48) and 5.17 months (95% CI, 4.58–5.75), respectively. In populations that usually do not meet the inclusion criteria of randomized studies, anti-PD-1-based therapy also showed favorable survival outcomes.

Various responses to ICBs by different tumor types mainly arise from the diversity of tumor immune microenvironments (32, 33). One of the well-investigated and commonly used biomarkers for systemic inflammatory response is circulating white blood cells, including neutrophils and lymphocytes (34, 35). Recent studies investigated the predictive value of NLR (neutrophil-to-lymphocyte ratio) and PLR for the treatment of checkpoint inhibitors. Low baseline NLR levels were associated with prolonged PFS and OS in metastatic melanomas following treatment with ipilimumab (CTLA-4) (36). In non-small cell lung cancers treated with anti-PD-1 inhibitors, low NLR and PLR levels were also reported to be associated with better PFS, OS, and response rate (37, 38). In our cohort, elevated NLR and PLR were predictive markers for OS in univariate analyses but not in multivariable analyses when considering clinical factors. This could have been partly explained by the small sample size, which might limit the statistical power.

In our cohort, combination therapy presented better survival outcomes in patients with liver metastases and elevated baseline NLR levels compared with anti-PD-1 monotherapy. The differences in PFS and OS between the treatment groups were no longer significant after adjusting according to clinical characteristics. In a recent update on the phase III study KEYNOTE-062, pembrolizumab combined with chemotherapy in gastric cancers as first-line therapy did not improve PFS or OS compared with pembrolizumab alone (15). In non-small cell lung cancer (NSCLC), anti-PD-1/L1 combined with chemotherapy showed better survival benefits than anti-PD-1/1 alone (39, 40). Tumor PD-L1 expression and the tumor immune microenvironment were previously reported to be affected by cytotoxic agents, which could explain the synergistic effects of the combination of anti-PD-1/L1

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TABLE 4 Safety and treatment-related adverse events.

		Monotherapy	Combination therapy	Hazard ratio(95%CI)	P value
	No. of patients	(n=19)	(n=35)		
Overall	54			0.70(0.36-1.35)	0.29
Gender					
Male	32	11	21	0.87(0.36-2.11)	0.75
Female	22	8	14	0.53(0.19-1.59)	0.24
Age					
<65	43	17	26	0.57(0.28-1.18)	0.13
≥65	11	2	9	1.40(0.16-12.05)	0.76
ECOG performance status					
0-1	36	8	28	0.80(0.31-2.11)	0.66
2-4	18	11	7	1.60(0.57-4.45)	0.37
Organs with metastases					
≤2	26	19	7	0.61(0.21-1.75)	0.36
>2	27	15	28	0.76(0.29-1.94)	0.56
Lymph node positive	47	18	29	0.79(0.39-1.60)	0.51
Peritoneum metastases					
Yes	31	13	18	1.12(0.42-2.30)	0.81
No	23	6	17	0.46(0.15-1.39)	0.17
Liver metastases					
Yes	27	5	22	**0.33(0.11-1.00)**	**0.05**
No	27	14	13	1.36(0.57-3.24)	0.48
Ascites					
Yes	25	10	15	1.00(0.40-2.00)	0.99
No	29	9	20	0.61(0.21-1.74)	0.35
Previous anticancer therapies for locally advanced/metastatic disease					
0-1	35	8	27	0.68(0.26-1.78)	0.43
≥2	19	11	8	0.60(0.20-1.79)	0.36
Previous gastrectomy					
Yes	22	15	7	0.59(0.16-2.12)	0.42
No	32	4	28	0.09(0.02-0.35)	0.00
Elevated LDH					
Yes	8	4	4	0.49(0.09-2.68)	0.41
No	46	15	31	0.76(0.36-1.62)	0.48
Elevated NLR					
Yes	26	9	17	0.38(0.14-1.00)	**0.05**
No	27	9	18	0.80(0.31-2.06)	0.64

(Continued)

TABLE 4 Continued

	No. of patients	Monotherapy (n=19)	Combination therapy (n=35)	Hazard ratio(95%CI)	P value
Elevated PLR					
Yes	26	10	16	0.42(0.17-1.04)	0.06
No	27	8	19	0.84(0.29-2.44)	0.75
HER2 positive					
Yes	10	5	5	1.97(0.32-12.31)	0.74
No	27	11	16	0.72(0.29-1.79)	0.48

ECOG, Eastern Cooperative Oncology Group.
LDH, lactate dehydrogenase.
NLR, neutrophil to lymphocyte ratio.
PLR, Platelet to lymphocyte ratio.
The meaning of the bold values was P value <0.05 and was considered statistically significant.

inhibitors and chemotherapy (41, 42). However, in the GC population, combination therapy's synergistic effects were relatively modest. Significant spatial heterogeneity of genomic alterations and tumor immune microenvironment in GC might account for inconsistent results and should be considered in future clinical trial designs (43, 44). There are several limitations to our study. Firstly, the sample size was limited. However, to our knowledge, this is one of the first real-world studies to explore the effectiveness and safety of anti-PD-1/L1 inhibitor monotherapy and combination therapy as first-line or second-line treatment in GC, especially in Asian patients. Second, this is a retrospective cohort study and could have been potentially biased. However, a retrospective real-world cohort allows us to investigate whether patients with higher ECOG scores or more advanced GC could benefit from immunotherapies, which is usually not feasible with prospective trials. Moreover, patients were recruited consecutively in an effort to minimize bias, and comprehensive clinicopathological information was collected to enable adjustment in multivariable regression analyses. Third, the combination regimens were heterogeneous, and a specific combination regimen should be considered when designing prospective studies in the future. Furthermore, the real-world study was very different from prospective clinical trials, and the subjects included in the real-world study were highly heterogeneous. For patients with GC, the heterogeneity of the tumor itself and its impact on the patient's physical condition, as well as their different physical status, treatment willingness, previous treatment history, economic status, drug availability, and other factors, affect the final treatment effect and survival outcomes. At the same time, due to the impact of the COVID-19 epidemic, the treatment of patients would be more or less affected, including whether they could come to the hospital to receive treatment during the prescribed time and the accessibility of drugs. The uncertainty of immunotherapy and the different methods of combination therapy also determined the heterogeneity and persistence of treatment.

On the other hand, real-world data played a vital role in perfecting and supplementing clinical research data. At the same time, we have seen whether immune monotherapy or combination therapy plays an important role, and the significance of this cannot be ignored in GC. Anti-PD-1 monotherapy and combination therapy showed promising survival outcomes and manageable safety profiles in advanced or metastatic GC/GEJCs in a real-world setting. Prolonged OS and PFS and increased ORR were observed in the combination group compared with the monotherapy group, although statistical significance was not reached. In some subgroups, such as patients with live metastases or elevated baseline NLR levels, combination therapy outperformed anti-PD-1 alone regarding survival outcomes. Treatment regimens involving anti-PD-1 in GC warrant further prospective investigations with larger sample sizes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

All participants in this study signed informed consent forms. The ethics committee of the People's Liberation Army General Hospital approved this study according to the ethical standards of the Declaration of Helsinki and its subsequent amendments (Ethical approval number:S2020-284-01). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TaL, TiL, and LZ served as co-first authors, with primary contributions to the manuscript. LL, XZ, and JW contributed to the acquisition, analysis, and interpretation of data. Study supervision: YH, FZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.976078/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan-Meier plot of overall survival in patients treated as first and second-line therapy.

SUPPLEMENTARY FIGURE 2
Kaplan-Meier plot of overall survival in patients treated as third-line or beyond therapy.

SUPPLEMENTARY FIGURE 3
Kaplan-Meier plot of progression-free survival in patients treated as first and second-line therapy.

SUPPLEMENTARY FIGURE 4
Kaplan-Meier plot of progression-free survival in patients treated as third-line or beyond therapy.

SUPPLEMENTARY TABLE 1
Univariate analysis and multivariate analysis for overall survival

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Peng Song,
Nanjing Drum Tower Hospital, China
Maher Hendi,
Sir Run Run Shaw Hospital, China
Beatrice Aramini,
University of Bologna, Italy

*CORRESPONDENCE
Qun Zhao
zhaoqun@hebmu.edu.cn

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The safety and efficacy of carbon nanoparticle suspension injection versus indocyanine green tracer-guided lymph node dissection during radical gastrectomy (FUTURE-01): A single-center randomized controlled trial protocol

Yuan Tian, Yue Pang, Peigang Yang, Honghai Guo, Yang Liu, Ze Zhang, Pingan Ding, Tao Zheng, Yong Li, Liqiao Fan, Zhidong Zhang, Xuefeng Zhao, Bibo Tan, Dong Wang and Qun Zhao*

Third Surgery Department, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Background: The use of lymph node (LN) tracers can help obtain a complete dissection of the lymph nodes and increase the detection rate of LNs and metastatic LNs. Carbon nanoparticle suspension injection (CNSI) and indocyanine green (ICG) have been widely used in radical gastrectomy in recent years. Nevertheless, the comparison of their clinical effects has not been studied.

Method/design: The FUTURE-01 trial will be the first randomized, open-label, single-center trial to compare CNSI and ICG. The study started in 2021 and enrolled 96 patients according to a prior sample size calculation. The primary outcome is the number of LNs retrieved. The secondary outcomes are LN staining rate, LN metastasis rate, stained LN metastasis rate, perioperative recovery and survival.

Conclusion: By comparing the safety and efficacy of CNSI and ICG tracer-guided LN dissection in patients with gastric cancer, we can determine the most appropriate LN tracer at present. With the help of LN tracers, the operation is simplified, and the prognosis of these patients is improved. Our

study is a prospective exploration of the safety, efficacy, and prognosis of CNSI and ICG.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT05229874?cond=NCT05229874&draw=2&rank=1, identifier NCT05229874.

KEYWORDS

clinical trial, design, gastric cancer, indocyanine green, lymph node, carbon nanoparticle suspension injection, gastrectomy, protocol

1 Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide (1). Despite the global downward trends in the GC incidence and mortality rates, GC remains one of the most common causes of death by cancer worldwide and ranks second (2).

For GC, complete resection with standardized LN dissection (D2) is important (3). Although LN dissection is deemed the crucial step in radical gastrectomy, there is no consensus regarding the number of LNs detected worldwide (4–6). The quality of LN dissection should be evaluated by the number of LNs detected, and more detection of LNs can reduce the N staging bias and prolong the GC patient prognosis (7–9).

D2 LN dissection is complex and tricky, and it is performed by removing perivascular fat and the LNs containing adipose baring fat tissue. In the process of lymphadenectomy in gastrectomy, one of the common and severe intraoperative complications is vessel injury. With the aim of easing the difficulty of LN dissection, an increasing number of surgeons are trying to use LN tracers to make the affected LNs distinct. Initially, surgeons used methylene blueand tattoo ink as LN tracers (10). Because of the difficulty of time limitations and low resolution, researchers have gradually abandoned the use of methylene blue.

Currently, two kinds of novel LN tracers have been monitored by endoscopy experts and surgeons. One is carbon nanoparticle suspension injection (CNSI), and the other is indocyanine green (ICG). In 2004, the CNSI (Carnaline, Chongqing Lummy Pharmaceutical Co., Ltd) made in China was launched, which reduced the price of CNSI and the cost medical expenditure and promoted the development of LN tracers. This product is a stable suspension of carbon nanoparticles 150 nm in diameter, which are smaller than the lymphatic capillary endothelial cell gap (120-500 nm) and larger than the capillary endothelial cell gap (30-50 nm) (11). Therefore, following their injection into the submucosa of the gastric wall around the tumor, the carbon nanoparticles rapidly captured by macrophages cannot enter into the blood vessels but enter into the lymphatic vessels and accumulate in the LNs (12). Moreover, CNSI with the features of black and strong colored ability makes the LNs more readily identified and makes the procedure easier. In addition, CNSI is characterized by slow metabolism and can be observed *in vivo* after approximately 3-4 months. Multiple studies have reported that CNSI has a respectably high safety profile, and no significant adverse effects were seen while the detection rate of LNs and metastatic LNs was increased (11, 13). Additionally, researchers have found no suggestion of increased complication rates or operating time.

ICG, as a kind of fluorescent dye, can be applied intraoperatively and used to sort LNs in postoperative specimens. When injected into the submucosa of the gastric wall of GC patients, ICG combines with serum albumin in the circulation and can be found in the LNs. Once excited by infrared light (wavelength, 750–810 nm), ICG can emit infrared fluorescence (peak wavelength, approximately 840 nm), so ICG fluorescence imaging can guide intraoperative LN dissection (14, 15). ICG fluorescence imaging can be performed successfully under a laparoscopic or robotic imaging system (16). Compared with other dyes, ICG fluorescence imaging with better tissue penetration has the potential to identify the LNs shaded by hypertrophic adipose tissue. ICG-guided D2 LN dissection has become a novel hot topic explored by an increasing number of gastrointestinal surgeons. In addition, ICG fluorescence imaging increases the number of LNs retrieved and exhibits a good clinical efficacy and safety profile (15–18).

Concerning the LN metastasis rates, there was not much difference between the CNSI, ICG, and control groups. Hence, we concluded that CNSI was more likely to be the best LN tracer at present. However, this is a retrospective single-center study that includes the well-known limitations of such a study design. It is therefore worthwhile to carry out a prospectively designed

study to compare the safety and efficacy of CNSI and ICG tracer-guided LN dissection during radical gastrectomy.

The present study therefore aims to compare the safety and efficacy of CNSI and ICG tracer-guided LN dissection during radical gastrectomy using a randomized clinical trial design and to provide a theoretical basis for further investigation.

2 Methods and analysis

2.1 Study design

The current study is a prospective, randomized, open label, single-center, noninferiority clinical trial. The study takes place in the Fourth Hospital of Hebei Medical University. Patient enrollment started on 20 January 2021, and the trial is expected to end on January 20 2025. Figure 1 summarizes the design of the trial, and each of the trial aspects is described in detail below.

2.2 Eligibility criteria

The inclusion criteria are as follows: (1) aged 18–75; (2) histologically proven gastric adenocarcinoma on biopsy (papillary adenocarcinoma, tubular adenocarcinoma, mucous adenocarcinoma, signet-ring cell carcinoma or poorly differentiated adenocarcinoma); (3) proven clinical stage of cT1-4a N0/+ M0 by ultrasound endoscopy, enhanced CT/MRI examination or diagnostic laparoscopy according to the TNM classification of the American Joint Committee on Cancer (AJCC cancer staging manual, eighth edition); (4) without distant metastasis and no invasion of adjacent organs; (5) a preoperative Eastern Cooperative Oncology Group (ECOG) score of 0 or 1; (6) a preoperative American Society of Anesthesiologists (ASA) score of I-III; and (7) signed a written informed consent form.

The exclusion criteria are as follows: (1) pregnant or lactating women; (2) patients with severe mental disorder; (3) a history of upper abdominal surgery (with exception of laparoscopic cholecystectomy); (4) a history of gastrectomies, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD); (5) enlarged or bulky regional LNs according to preoperative imaging and larger than 3 cm at the long diameter; (6) the tumor invades the duodenum or esophagus; (7) Borrmann type IV GC; (8) history of other malignant tumors within the last 5 years; (9) received previous neoadjuvant radiotherapy or chemotherapy; (10) history of myocardial infarction or unstable angina within the last 6 months; (11) history of cerebrovascular accident within the last 6 months; (12) undergoing sustained systemic corticosteroid treatment within 1 month prior to surgery; (13) emergency surgery due to GC complications (bleeding, perforation, or obstruction); and (14) FEV1 <50% predicted value.

2.3 Randomization and blinding

The patients were enrolled by a dedicated surgeon on our team. For eligible patients treated with GC at The Fourth Hospital of Hebei Medical University, thoracoabdominal CT, echocardiography, ultrasound of supraclavicular LNs, sonography of lower extremity veins, electrocardiogram and lung function examination should be performed before the operation. The patients who meet the inclusion criteria and are feasible for radical onco-surgery are then randomized to receive either endoscopic injection of CNSI (CNSI group) or endoscopic injection of ICG (ICG group) during gastroscopy at a 1:1 ratio. Randomization has been achieved using a random number table by the data manager, and the allocation is not concealed. While the blinding of the surgeons or participants is impossible, the pathologists are blinded to the types of surgical approaches.

2.4 Interventions

In the CNSI group, the patients are given injections of CNSI (50 mg/dose) produced by Chongqing Lummy Pharmaceutical Co., Ltd. in the endoscopy division 1 day before surgery. CNSI is injected submucosally at 4 points (proximal side, distal side, and left and right sides) 0.5-1 cm from the tumor edge under endoscopy. The optimized dose for each point is approximately 0.25 ml (Figure 2A).

For those who were randomly assigned to the ICG group, ICG (25 mg/dose) produced by Dandong Yichuang Pharmaceutical is marked in the endoscopy division 1 day before surgery and is injected submucosally at 4 points (proximal side, distal side, and left and right sides) 0.5-1 cm from the tumor edge under endoscopy. The optimized dose for each point is approximately 0.5 ml (Figure 2B).Both procedures are performed by a designated, experienced endoscopic specialist.

Laparoscopic exploration and detection of free peritoneal cancer cells are necessary in the first step of the surgical procedure to exclude adjacent organ infiltration and peritoneal metastasis. When the patient is positioned in the reverse Trendelenburg position (described as the foot-down and head-up supine position), 800 ml of normal saline is routinely used to wash the area near the carcinomatous foci of GC and is then re-collected as much as possible. It is important to collect at least 300 ml of the flushing fluid from the pelvic cavity. Cytology examination is then immediately performed on the flushing fluid collected. If the peritoneum is free of metastasis and peritoneal lavage cytology is negative, standard laparoscopic or robotic radical gastrectomy with D2 lymphadenectomy is then performed by the designated and experienced team of surgeons according to the Japanese Gastric Cancer Treatment

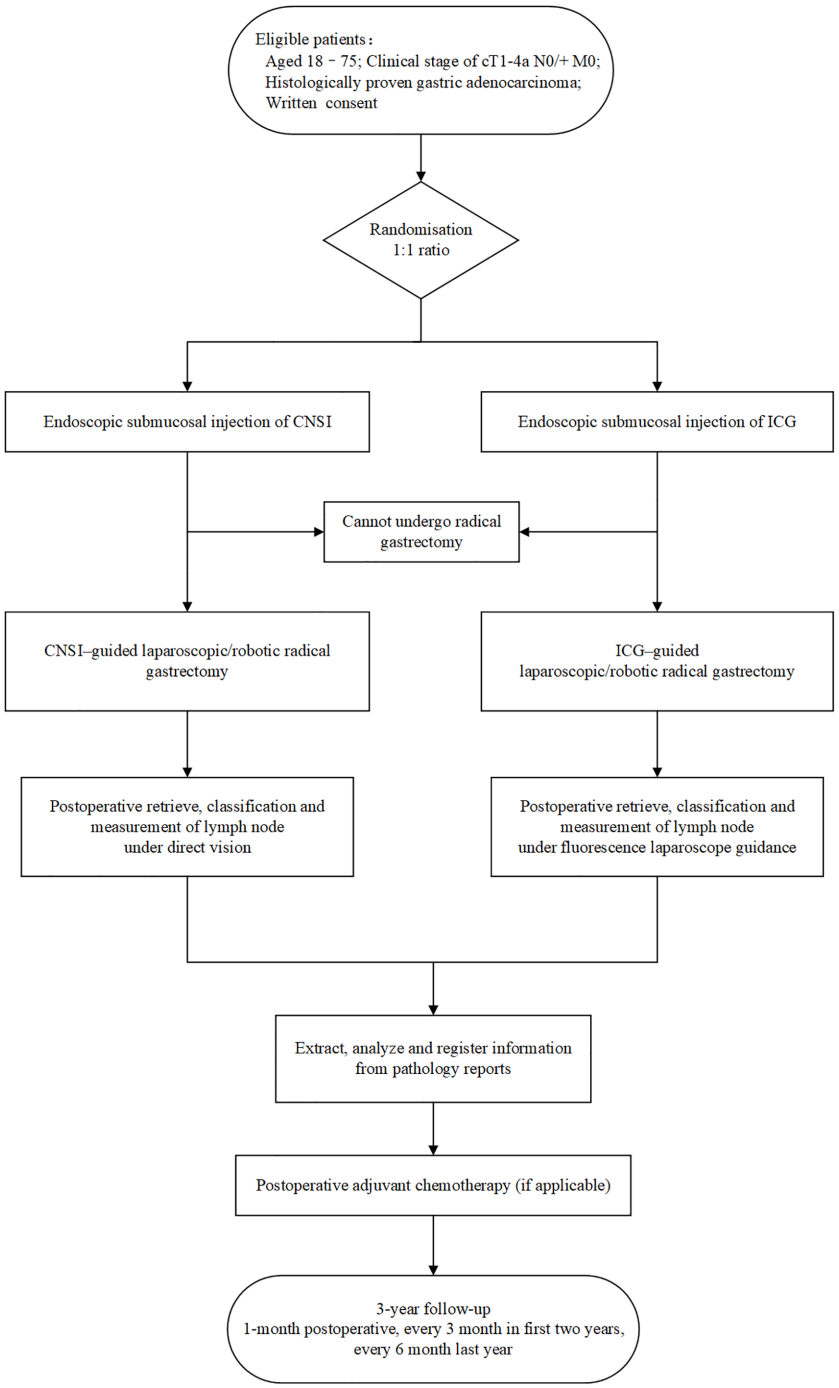

FIGURE 1
Flow chart.

Guidelines 2014. Distal gastrectomy for LN dissection included LN station 1, 3, 4 sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a.

Before starting to retrieve LNs from the GC patients, the surgeon should determine the positions of each station LN on the specimen in detail and plan the sequence of retrieving the LNs. After washing and flattening the specimen, we began to retain the soft tissues of each station of LNs by cutting off the useless tissues in the specimen (Figure 3). Then, after observing the course of the artery encased in fatty tissue and removing the perivascular fat, we dissected the LNs arranged along the

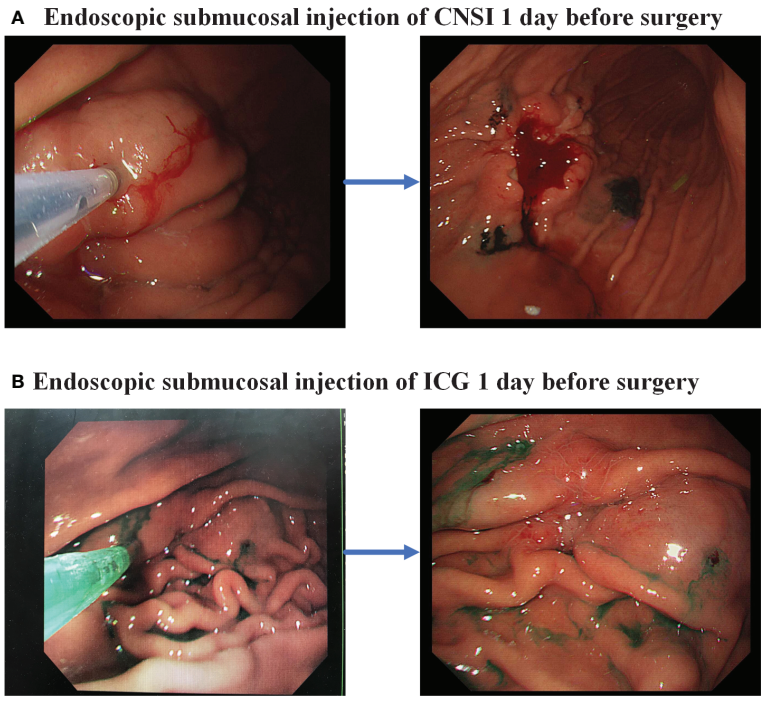

FIGURE 2
Endoscopic injection of lymph node tracer. **(A)** Carbon nanoparticle suspension injection; **(B)** Indocyanine green.

vascular lumen. Dissecting the LNs must be completed within 30 minutes after the specimen is detached. The dissected LNs, which are fixed with formalin, were then separated by the different LN stations, the staining status and the LN maximum diameter (>2 or ≤2 mm) and sent to the pathology department for histopathological study. The surgeon appointed to the dissection of the LNs must have a thorough grasp of the knowledge about LNs and abundant experience.

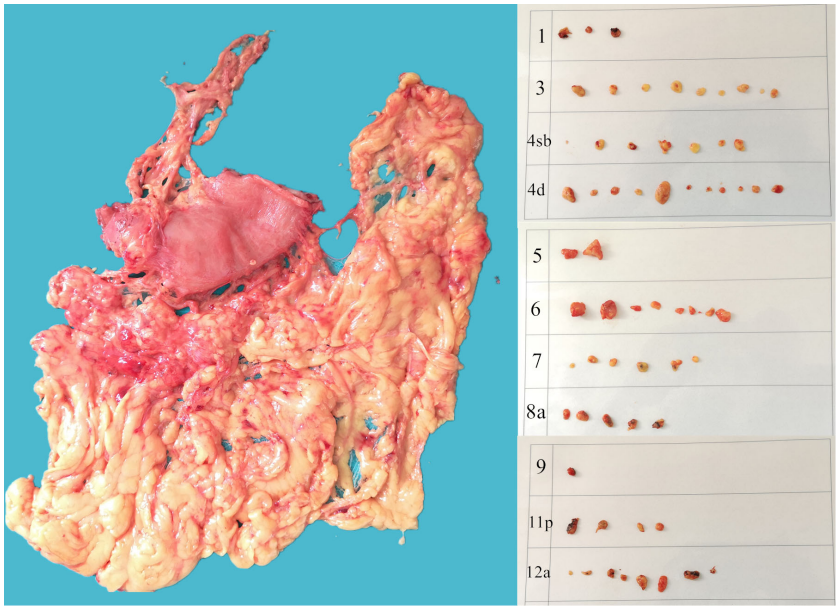

FIGURE 3
The lymph nodes after dissecting the lymph nodes from specimen.

2.5 Outcomes

The primary outcome of this study is to determine the number of LNs retrieved. The secondary outcomes are to determine the LN staining (or fluorescence) rate (Number of staining or fluorescence LNs/Total number of retrieved LNs), LN staining (or fluorescence) rate at each station, stained (or fluorescent) LN positive rate(Number of staining or fluorescence positive LNs/Total number of positive LNs), stained (or fluorescent) LN negative rate(Number of staining or fluorescence negative LNs/Total number of negative LNs), nonstained (or nonfluorescent) LN positive rate(Number of nonstaining or nonfluorescence positive LNs/Total number of positive LNs), nonstained (or nonfluorescent) LN negative rate (Number of nonstaining or nonfluorescence negative LNs/Total number of negative LNs), LN metastasis rate(Number of metastasis LNs/Total number of retrieved LNs), number of metastatic LNs, complication and mortality rates within 30 days, 3-year disease-free survival (DFS), 3-year overall survival (OS), recurrence pattern within 3 years, intraoperative blood loss volume, time spent retrieving LNs, and postoperative recovery (exhaust time after surgery, feeding time after surgery, duration of postoperative hospital stay).

Any complications should be recorded and reported. There are mainly two complications related to the procedure: intraoperative complications and postoperative complications. The former includes bleeding, injuring the viscera, lymphatic leakage and so on. The latter should be classified according to the Clavien–Dindo classification system.

2.6 Adverse events

Adverse events (AEs) refer to patient injuries caused by medical care (19). Serious adverse events (SAEs) refer to medically related events that result in death, are life-threatening, require hospital admission or prolong hospital stay, or cause persistent or significant disability. Although adverse effects of CNSI and ICG have not been observed in preclinical studies, any forms of adverse events should be systematically recorded.

2.7 Sample size

The sample size for this study was calculated based on previous research by our team and computed by PASS version 11. Eligible subjects were randomly assigned (1:1) into the CNSI group and the ICG group. All analyses were two-sided with α=0.05 and β=0.80. the prospective mean number of the LNs retrieved in the CNSI group was 56.93. The prospective mean number of the LNs retrieved in the ICG group was 50.52. The total sample size was 96 (48 per group) after taking into account a 10% dropout rate in each group. The planned recruitment period is 1 year, and the follow-up duration is 3 years.

2.8 Data collection and analysis

Designated and trained surgeons collect the data from the pathology reports and operative reports. The focus of the data should contain clear information about the tumor location, tumor size, histopathologic type, tumor differentiation degree, Lauren classification, vascular tumor embolus, nerve invasion, immunohistochemistry results and pathological findings of the LNs at each station. Long-term prognosis data are collected *via* follow-up up until 3 years after the surgical operations. The follow-up should consist of a 3-month interval from 0–2 years and a 6-month interval in the third year. The main follow-up items included routine physical examination, tumor marker detection (CEA, CA199, CA724 and AFP), abdominal CT, and annual electronic gastroscopy. The follow-up included an outpatient follow-up, a telephone follow-up and a short message platform follow-up. Further evaluation and treatment should be performed if relapse occurs.

The purpose of this study is to compare the safety and efficacy of CNSI and ICG during radical gastrectomy. The primary objective is to determine the number of LNs retrieved. Comparability analysis will be performed on the baseline data to determine whether the two groups are comparable. The number of patients, mean, standard deviation, median, maximum, and minimum will be listed. Descriptive data will be presented as the mean ± SD, while categorical data will be presented as the number and percentage (%). The independent samples t test or nonparametric test will be used to analyze continuous data, and the chi-square test or Fisher's exact test will be used to analyze categorical variables. It is valuable to analyze the influence of CNSI (ICG) staining or other factors on the number of LNs detected according to the statistical analysis. We can also research the effect of CNSI (ICG) staining on the operative time, intraoperative bleeding volume, intraoperative transfusion volume and postoperative complications. Survival analysis will be performed using the Kaplan–Meier method, and the log rank test will be used to test the difference in survival rates between the two groups. SPSS 26.0 statistical software will be used for statistical analysis. $P<0.05$ will be considered to indicate statistically significant differences.

3 Discussion

Despite the serious burden of GC in China, the public awareness of risk factors or warning symptoms and screening is low, and there is a lack of screening programs (20). Therefore, the majority of GC are detected at an advanced stage, and at this

moment, LN metastasis usually occurs. It is well known that LN metastasis is one of the most important prognostic factors for GC patients, and D2 LN dissection has gradually become the mainstream treatment to improve patient outcome (21). The mean number of LNs dissected in Western European countries was 29.5, which is slightly higher than that in China (22). This condition might be associated with the insufficient LN dissection intraoperatively and the false idea that postoperative LN dissection should be completed by a pathologist. Currently, an increasing number of studies have begun to focus on LN tracers, and an increasing number of gastrointestinal surgeons have started using carbon nanoparticle suspension injection or indocyanine green.

A number of interesting differences were identified through our analyses of CNSI and ICG. First, taking an appropriate amount of time to dissect LNs as an example, the LNs are stained black using CNSI, while the LNs labeled with ICG have the ability to generate strong fluorescence emission in certain cases. When utilizing CNSI as a tracer of LNs, surgeons can dissect the LNs under direct vision without the assistance of other instruments. However, if surgeons intend to use indocyanine fluorescence imaging to guide the postoperative nodal dissection, the fluorescence imaging mode must be available, and the wear and tear of the instrument and the burden on surgeons and operating room nurses will increase, which may prolong the time needed for dissecting the LNs. Second, compared with CNSI, ICG may have the potential to decrease the risk of anastomotic fistula with the assistance of examining the blood supply of the anastomosis. Third, CNSI extravasation into gastric serosa will contaminate the surgical fields and increase the difficulty of surgically dissecting the gastric tumor, but surgeons can switch between the fluorescence mode and normal mode to avoid the adverse effects caused by ICG extravasation (15).

There are a number of previous reviews on the effectiveness of CNSI and ICG. Chen pointed out that their team analyzed 129 GC patients in the ICG group and 129 control subjects and concluded that ICG tracer-guided LN dissection enabled the retrieval of a higher number of LNs (16). Two retrospective analyses found that fluorescence lymphography has high sensitivity and negative predictive value for the diagnosis of LN metastasis. Fluorescent lymphography-guided lymphadenectomy appears to be a reasonable alternative to conventional systematic lymphadenectomy for gastric cancer (23, 24). Similarly, in accordance with the study of Yan, carbon nanoparticles have the same efficacy and safety as a LN tracer in the clinic (11). Li et al. and our team found that CNSI is a safe material. Surgeons could harvest more LNs in patients with GC. The harvest of an increased number of smaller diameters of LNs may be beneficial. CNSI is associated with facilitating the dissection of all positive LNs, which could improve surgical quality (13, 25). However, very few studies have focused on the comparison of CNSI and ICG. A retrospective study recently conducted by our team suggested that the mean numbers of LNs and micro LNs retrieved in the CNSI group were higher than those in the ICG and control groups, and there were no differences between the ICG and control groups (15).

Whether the results of retrospective analysis can be confirmed by prospective randomized controlled clinical trials still needs to be further studied. Therefore, we are currently conducting a clinical trial to compare CNSI and ICG in detail to choose the optimal and suitable LN tracer for radical gastrectomy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee of Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: QZ and YT. Data curation: YT, YP, PY, HG, YaL, ZeZ, PD, and TZ. Investigation and experiments: YoL, LF, ZhZ, XZ, BT, DW, and QZ. Methodology: YT. Formal analysis: YT, YP, and PY. Supervision: QZ. Writing – original draft: YT and YP. Writing review and editing: YoL, LF, ZhZ, XZ, BT, DW, and QZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Edouard Auclin,
Hôpital Européen Georges-Pompidou, France

REVIEWED BY
Feng Cao,
Xuanwu Hospital, Capital Medical University, China
Giuseppe Zimmitti,
Fondazione Poliambulanza Istituto Ospedaliero, Italy

*CORRESPONDENCE
Zhao-Shen Li
zhaoshenli@hotmail.com
Liang-Hao Hu
lianghao-hu@smmu.edu.cn

†These authors have contributed equally to this work

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Transparency of clinical trials in pancreatic cancer: An analysis of availability of trial results from the ClinicalTrials.gov database

Ren-Qian Huang[1,2†], You Zhou[2,3†], Hai-Xia Zheng[1†], Dan Wang[2], Xiao-Yi Zheng[1,2], Zhao-Shen Li[2*] and Liang-Hao Hu[2*]

[1]Postgraduate training base in Shanghai Gongli Hospital, Ningxia Medical University, Shanghai, China, [2]Department of Gastroenterology, First Affiliated Hospital of Naval Medical University, Shanghai, China, [3]Pancreatic Center, Department of Gastroenterology, Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, Jiangsu, China

Background: Pancreatic cancer (PC) is a highly malignant tumor of the digestive system. As clinical trials involving PC are increasingly being conducted, the transparency of the generated data has become an important issue of concern. In other areas of medicine, clinical trial transparency presents a worrying state of affairs. However, at present, there has been no study examining the transparency of data derived from PC clinical trials.

Methods: A comprehensive search was conducted in the ClinicalTrial.gov database for clinical trials investigating pancreatic cancer as of June 2022. We examined the availability of clinical trial results and recorded the characteristics of the trials.

Results: A total of 856 trials were included in this study, of which 668 were completed and 188 were terminated or suspended. The results of 626 trials (73.13%) were available, of these 230 trials (26.87%) did not disclose any information on the trial data in any form. The publication rate for trials with available results was 86.10%, but the report rate on ClinicalTrial.gov was only 39.78%.

Conclusion: Although approximately 90% of clinical trial investigating interventions on patients with PC have published study results, 30% of trials did not report any findings, and the disclosure of trial results from ClinicalTrial.gov was unsatisfactory. In general, there is still room for improvement in the transparency of PC clinical trials.

KEYWORDS

transparency, Clinicaltrials.gov, clinical trials, publication of results, pancreatic cancer

1 Introduction

The lack of transparency in clinical trials is a long-standing concern that has attracted much attention (1). In 1997, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) collaborated to develop ClinicalTrials.gov, which was later promoted worldwide and finally made available to the public in 2000 (2). ClinicalTrials.gov was designed to provide clinicians worldwide with detailed information about clinical trials on a variety of diseases. Initially, clinical trials were required to be registered within 21 days of enrolling the first subject and the submission of the trial results was not mandatory (3). However, the results of some clinical trials (e.g., trials not meeting the primary endpoint) and adverse events may have been selectively disclosed due to the interests of the study sponsor, leading to undesirable consequences such as limiting knowledge dissemination and understanding of the clinical benefits and harms to patients (4). Therefore, to address this issue, Section 801 of the US Food and Drug Administration Amendments Act (FDAAA) of 2007 expanded the legal requirements for trials on ClinicalTrials.gov, in which trials were required to report results within one year after completion, regardless of whether the trial results had been published (5). However, several studies have found that most researchers ignore this provision. In a transparency study in clinical gastroenterology trials, results were available for 1824 of a total of 2429 clinical trials, but only 29% were disclosed on ClinicalTrials.gov (6). In another study on the transparency of clinical trials of gastrointestinal endoscopy studies, results were available for 751 of 923 trials and only 22% were reported on ClinicalTrials.gov (7).

Pancreatic cancer (PC) is a highly malignant tumor of the digestive system and is one of the leading causes of death among cancer patients worldwide (8, 9). The prognosis for PC is poor, with overall survival rates of 24% and 9% at 1 and 5 years, respectively (10). In the United States, PC ranks fourth in malignancy-related deaths, while in China, PC ranks sixth (11, 12). In recent years, the diagnosis and treatment of PC have been further improved with the continuous development of endoscopic techniques, imaging, and pathology, as well as advances in antitumor drugs, radiotherapy techniques, and surgical concepts (13–16). In this process, a large number of clinical trials on PC have been conducted in countries around the world. The disclosure of clinical trial results, whether good or bad, is critical for researchers, clinicians, and patients. It can help researchers design research schemes and assist clinicians in formulating better treatment schemes for patients. However, in the field of PC, there is still a lack of relevant studies on the transparency of clinical trials.

Therefore, the objective of this study was to assess the availability of clinical trials results related to studies on PC registered on the ClinicalTrials.gov database.

2 Methods

2.1 Search strategy and data sources

Based on the advanced search function of ClinicalTrials.gov, we used the search terms “pancreatic tumor” and “pancreatic cancer” on 1 June 2022 to retrieve eligible trials. We did not set restrictions on the search terms to include as many clinical trials as possible.

2.2 Eligibility criteria

Clinical trials were enrolled in this study if they met the following inclusion criteria (1): all registered adult clinical trials showing completion, suspension, or termination as of 1 June 2020 (Referring to previous studies, a two-year follow-up period was allowed to disclose the results of clinical trials (7)) (2); clinical trials on PC.

The exclusion criteria were as follows (1): non-PC clinical trials (2); clinical trials involving children (3); clinical trials showing other statuses except for completion, suspension, and termination (4); clinical trials without specific completion time.

2.3 Data extraction and transparency of studies

Based on the information provided by ClinicalTrials.gov, such as the NCT number, trial title, trial purpose, intervention method, study site and researcher, three authors (RQH, YZ, and HXZ) searched the PubMed, Google Scholar, and Web of Science database for trial results published in peer-reviewed journals. Furthermore, based on the reference links in ClinicalTrials.gov, we also considered that the trial results were published if the contents of publication were consistent with the contents of the trial registration. Any disagreements were resolved through the authors’ consultation.

The following characteristics of clinical trials were recorded: availability of results, registration date, duration of trials, type of study, study status, type of intervention, phase of study, source of funding, type of endpoints, whether or not the primary endpoint was met, number of study sites, country of origin and reasons for suspension and termination of trials.

2.4 Statistics

First, we divided all included trials into two groups based on the availability of the trial results. Univariate analysis was used to compare significant differences in trial characteristics between the two groups. Multivariate logistic regression analysis was used

to identify characteristics that were independently associated with the availability of the results of the clinical trial. The effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Furthermore, trials with available results, were divided into two groups based on whether they met the primary endpoint and were then compared the disclosure rate of results on ClinicalTrials.gov and the publication rate in peer-reviewed journals between the two groups. All statistical analyses were performed using SPSS 26.0 software. Categorical variables were expressed using frequencies and proportions and analyzed using Pearson's χ^2 test. Continuous variables were expressed using the median and interquartile range and analyzed using the nonparametric Mann-Whitney test. A *P*-value <0.05 was considered statistically significant.

3 Results

3.1 Search results

Figure 1 shows the selection process for clinical trials. A total of 3156 trials related to PC were extracted from ClinicalTrials.gov during the initial search, of which 1593 were excluded because of study status, 276 were excluded due to the date of completion, 19 were excluded for including children, and 412 were excluded because they were not trials involving only pancreatic malignancies. Ultimately, 668 completed trials and 188 terminated or suspended trials were used for statistical analysis.

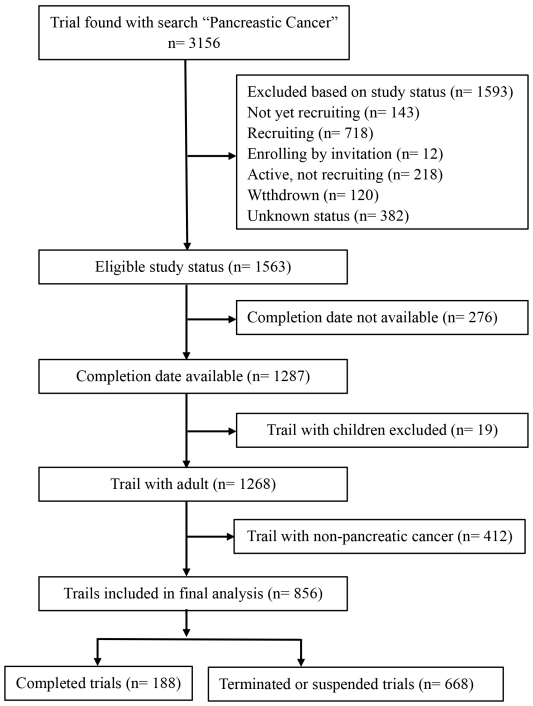

FIGURE 1
Flow diagram of clinical trials selection..

3.2 Trial characteristics

Table 1 presents the characteristics of the included clinical trials. Of a total of 856 trials, study results were available for 626 trials, of which 249 (249/626, 39.78%) had results disclosed on ClinicalTrials.gov, 539 (539/626, 86.10%) had results published in peer reviewed journals, and 164 (164/626, 26.20%) were both disclosed on ClinicalTrials.gov and published in peer-reviewed journals. Of the 626 trials with available results, 541 (86.42%) met the primary endpoint. The results of these studies were presented most often in the form of publications (*P*<0.001) and studies not meeting the primary endpoint rarely disclosed the results on ClinicalTrials.gov (*P*<0.001). Interventional trials (578/757, 76.35%) were more likely to have available results than observational trials (48/99, 48.48%) (*P*<0.001). Compared to suspended or terminated trials (112/188, 59.57%), completed trials (514/668, 76.95%) were more likely to report results (*P*<0.001). In comparison, intervention-type trials associated with chemotherapeutic drugs and biological therapies were more likely to have results (*P*<0.001). Phase II studies and the above trials were more likely to report results than trials with unknown phase status or Phase I trials (*P*<0.001). Trials with clinical endpoints (525/683, 76.87%) were more likely to disclose results than trials with nonclinical endpoints (101/173, 58.38%) (*P*<0.001). Compared to single-center trials (327/479, 68.27%) or those with an unknown study site (33/49, 67.35%), multicenter trials (266/328, 81.10%) were more likely to report results (*P*<0.001). Furthermore, trials with longer duration had a higher frequency of disclosed results (*P*<0.001). There were no significant differences in the availability of trial results in terms of the completion date before or after 1 January 2008, source of funding, the country of trial origin, and reasons for trial termination or suspension.

3.3 Contributing factors of results availability

Table 2 shows the results of the logistic regression analysis. Compared to observational trials, interventional trials had better availability of the results (OR=2.591, 95% CI 1.297-5.180, *P*=0.007). Completed trials had higher availability of results than terminated or suspended trials (OR=2.624, 95% CI 1.796-3.834, *P*<0.001). Drug-related trials were more likely to disclose the results of trials than trials with unknown interventions (OR=3.758, 95%CI: 1.299-10.980, *P*=0.015). Phase II trials (OR=2.512, 95% CI 1.630-3.873, *P*<0.001) and trials with

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TABLE 1 Characteristics of included clinical trials investigating PC.

Total trials (n=856)	Results available (n=626)		Results not available (n=230)	*P*-value
Before 1 January 2008	219 (34.98)		89 (38.70)	0.316
After 1 January 2008	407 (65.02)		141 (61.30)	
Primary endpoint met (%)	No (n=85)	Yes (n=541)		
1. Registered on clinicaltrials.gov				
a. Yes	36 (42.35)	213 (39.37)		0.602
b. No	49 (57.65)	328 (60.63)		
2. Published results				
a. Yes	55 (64.71)	484 (89.46)		< **0.001**
b. No	30 (35.29)	57 (10.54)		
Study type				
1. Interventional	578 (92.33)		179 (78.11)	< **0.001**
2. Observational	48 (7.67)		51 (22.17)	
Study status				
1. Completed	514 (82.11)		154 (66.96)	< **0.001**
2. Terminated or suspended	112 (17.89)		76 (33.04)	
Intervention				
1. Procedure	52 (8.31)		36 (15.65)	< **0.001**
2. Device	23 (3.67)		10 (4.35)	
3. Drug	415 (66.29)		109 (47.39)	
4. Radiation	23 (3.67)		9 (3.91)	
5. Biological	64 (10.22)		20 (8.70)	
6. Other	39 (6.23)		30 (13.04)	
7. Unknow	10 (1.60)		16 (6.96)	
Phase				
1. I	104 (16.61)		57 (24.78)	< **0.001**
2. II	340 (54.31)		70 (30.43)	
3. III	52 (8.31)		17 (7.39)	
4. IV	4 (0.64)		4 (1.74)	
5. Unknow/not available	126 (20.13)		82 (35.65)	
Funding source				
1. NIH or Federal	21 (3.35)		6 (2.61)	0.376
2. Industry	150 (23.96)		46 (20.00)	
3. Other	455 (72.68)		178 (77.39)	
Endpoint				
1. Clinical	525 (83.86)		158 (68.70)	< **0.001**
2. Non-clinical	101 (16.13)		72 (31.30)	
Centers				

(Continued)

TABLE 1 Continued

Total trials (n=856)	Results available (n=626)	Results not available (n=230)	*P*-value
1. Single	327 (52.24)	152 (66.09)	< **0.001**
2. Multiple	266 (42.49)	62 (26.96)	
3. Unknow	33 (5.27)	16 (6.96)	
Country of trial origin			
1. North America	357 (57.03)	135 (58.70)	0.616
2. Europe	118 (18.85)	42 (18.26)	
3. Asia	59 (9.42)	23 (10.00)	
4. Multiple countries	54 (8,63)	12 (5.22)	
5. Other	5 (0.80)	2 (0.87)	
6. Unknown	33 (5.27)	16 (6.96)	
Median trial duration in weeks (IQR)	3.75 (2.41, 5.42)	3.00 (1.92, 4.70)	< **0.001**
Reason for termination or suspension of trial (n=188)			
1. Enrolment issues	10 (8.93)	4 (5.26)	0.700
2. Safety concerns, adverse events, interim analysis	16 (14.29)	8 (10.53)	
3. Medical futility or lack of efficacy	19 (16.96)	11 (14.47)	
4. Issues related to funding, personnel, supplies, local or federal regulation	35 (31.25)	28 (36.84)	
5. Unclear	32 (28.57)	25 (32.89)	

Bold text indicated the statistical difference of the P value between groups.

unknown or not available Phase details (OR=2.982, 95% CI 1.465-6.069, P=0.003) had better results availability than phase I trials. Furthermore, the duration of the trial in years was found to be a contributing factor in the availability of the results (OR=1.070, 95%CI: 1.000-1.145, *P*=0.050).

4 Discussion

Public disclosure of clinical trial results is important both for clinical decision-making and for dissemination of knowledge (17). However, due to the complexity and unknown outcomes of clinical trials and the inattention of some study coordinators, the current availability of clinical trial results is not satisfactory in many fields (18). To identify the disclosure rate of clinical trial results in PC, we conducted this study and analyzed relevant factors that may affect the availability of clinical trial results. Our study provided preliminary evidence for the transparency of PC clinical trials and provided a reference for the design and development of PC clinical trials in the future.

In terms of clinical trials with available results, we found that 86.10% (539/626) eventually reported their findings in publications, but only 39.78% (249/626) reported the results on ClinicalTrials.gov. While a publication rate of approximately 90% was satisfactory, a 40% reporting rate of results on ClinicalTrials.gov suggested that most researchers seemed to have ignored the significance of ClinicalTrials.gov for information disclosure of clinical trial results and there was still room for improvement in the disclosure of PC clinical trial results. Given the current open-access policy for journals, ClinicalTrials.gov remained a more rapid, efficient, and less expensive option for accessing trial results. Therefore, we suggested that sponsors of clinical trials, publishers and editors of journals should strengthen their review of ClinicalTrials.gov during the development of clinical trials and on the submission of articles for publication to ensure that all clinical trial results were disclosed on ClinicalTrials.gov. In addition, we found that 26.87% of the trials did not disclose any information about the results. Similar results have been found in previous studies. In one study evaluating the transparency of clinical trials in ovarian cancer, about 25% of the results of clinical trials were not published in any form (19). Nguyen et al. found that approximately half of US cancer drug trials were not published three years after the trials were completed (20). This indicated that, in addition to PC, clinical trials in other cancer fields also have some problems with transparency. Owing to the highly malignant nature and the extremely low long-term survival rate of PC, timely disclosure of the results of clinical trials is of great importance. On the one hand, trials that meet the primary endpoint can help clinicians better formulate the treatment of

TABLE 2 Multivariate logistic regression for influencing factors of the availability of PC clinical trial results.

Trial characteristics	OR (95% CI)	*P* value
Interventional vs. observational	2.591 (1.297, 5,175)	**0.007**
Completed vs. terminated or suspended	2.624 (1.796, 3.834)	**<0.001**
Intervention		
1. Procedure	1.534 (0.564, 4.175)	0.402
2. Device vs. unknown	1.691 (0.484, 5.902)	0.410
3. Drug vs. unknown	3.758 (1.299, 10.980)	**0.015**
4. Radiation vs. unknown	2.763 (0.771, 9.905)	0.119
5. Biological treatment vs. unknown	2.780 (0.863, 8.956)	0.087
6. Other treatment vs. unknown	1.486 (0.550, 4.012)	0.435
Phase		
1. II vs. I	2.512 (1.630, 3.873)	**<0.001**
2. III vs. I	1.594 (0.804, 3.161)	0.182
3. IV vs. I	0.579 (0.130, 2.587)	0.475
4. Unknown/not available vs. phase I	2.982 (1.465, 6.069)	**0.003**
Clinical vs. Non-clinical	1.318 (0.835, 2.081)	0.235
Centers		
1. Multiple vs. single	1.437 (0.981, 2.103)	0.062
2. Unknow vs. single	0.902 (0.452, 1.802)	0.771
Median trial duration in years (IQR)	1.070 (1.000, 1.145)	**0.050**

Bold text indicated the statistical difference of the P value between groups.

patients to delay disease progression and improve prognosis; on the other hand, failed trial results or adverse reactions in trials can prevent the continuation of such studies and harm to patients in treatment. Therefore, we believe that irrespective of the results of clinical trials, researchers should comply with the FDAAA and establish knowledge sharing and report the content and results of the trial in a timely manner to improve the transparency of data derived from clinical trials.

In this study, we also identified characteristics of clinical trials that were associated with the availability of results, such as interventional trials, completed trials, drug-related trials, phase II trials, and trials of longer duration, which may provide an important reference for researchers when designing trial protocols. We believed that compared with observational studies, the process of recruitment and ethical review of interventional studies are more complex and stricter, and the disclosure requirements for them are also higher, which may be one of the reasons for the high availability of results. Compared to completed studies, we found that more terminated or suspended studies failed to disclose information about trial results on ClinicalTrials.gov (40.43% VS. 23.05%). Researchers seemed to neglect the disclosure of trial information because of the interruption of the study process. In addition, drug-related interventions were found to be significantly correlated with the availability of trial results in our study. Considering the high malignancy of PC, patients still have a high risk of recurrence and a poor prognosis even after radical resection. At present, chemotherapy protocols based on fluorouracil have become the standard treatment strategy for PC worldwide (21). To improve the disease condition and prognosis of patients, many large-scale clinical trials of perioperative and advanced first-line chemotherapy for PC patients are being carried out (22). Therefore, drug-related clinical trials had a higher disclosure rate regardless of trial results. Although the introduction of the FDAAA in 2007 did not have a significant impact on the availability of results in this study, it was undeniable that a higher proportion of trials registered after 1 January 2008 disclosed their study results (65.02% vs. 61.30%). It can be seen that the FDAAA did have a certain positive significance for improving the transparency of clinical trials. Additionally, 40.43% (76/188) of the terminated or suspended trials did not report any results. In future, researchers should pay closer

attention to the reasons for changes in the progression of the trials and report their findings in a timely manner to avoid unnecessary waste of resources and adverse effects on patients.

This study also has certain limitations. We only included PC-related clinical trials registered on ClinicalTrials.gov for analysis, and clinical trial registration platforms in other countries or not in English were not included in our study, which may lead to certain selection bias. Based on our study, future studies should expand eligibility criteria and include more clinical trial registration platforms to enrich findings.

5 Conclusions

This study was the first to examine the transparency in the divulgation of data obtained from clinical trials involving patients with PC. Approximately, 26.87% of clinical trials did not disclose any information about their results and of the trials with available results, 60.22% did not disclose findings on ClinicalTrials.gov. Overall, there is still room for improving the transparency data deriving from clinical trials involving patients with PC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

L-HH was the principal investigator for this project and made critical revisions to the article. R-QH, YZ and H-XZ were responsible for analyzing and interpreting the data and drafting the manuscript. DW and X-YZ assisted in data collection, analysis. Z-SL and L-HH supervised the research process and provided technical suggestions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1026268/full#supplementary-material

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EDITED BY
Salvatore Siracusano,
University of L'Aquila, Italy

REVIEWED BY
Hong Zhu,
Sichuan University, China
Chunxia Su,
Shanghai Pulmonary Hospital, China

*CORRESPONDENCE
Yongping Yang
yongpingyang@hotmail.com
Zhen Zeng
zengzhen1970@sina.com

†These authors have contributed equally to this work

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Age independent survival benefit for patients with small hepatocellular carcinoma undergoing percutaneous cryoablation: A propensity scores matching study

Huixin Zhang[1†], Muoyan Xu[2†], Jiashen Shao[3†], Huifang Kong[1†], Xudong Gao[1†], Wei Zhang[1], Xiujuan Chang[1], Bin Yang[1], Yan Chen[1], Zheng Dong[1], Jiagan Huang[1], Zhen Zeng[1*] and Yongping Yang[1*]

[1]Department of Liver Diseases, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China, [2]Healthcare Office of Chinese PLA General Hospital, Beijing, China, [3]Department of Orthopedics, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Background: Hepatocellular carcinoma (HCC) is the major cause of malignancy-related deaths worldwide, and its incidence is likely to increase in the future as life expectancy increases. Therefore, the management of elderly patients with HCC has become a global issue. Aim of this study was to assess whether elderly patients with small HCC could obtain survival benefit from cryoablation (CRYO) in a real-world.

Materials and methods: From July 2007 to June 2013, 185 patients with small HCC who underwent curative-intent percutaneous CRYO. All patients were divided into three groups according to age distribution. Overall survival (OS) and tumor-free survival (TFS) were compared between among of groups before and after the 1:1 propensity score matching, respectively. Univariate and multivariate Cox analyses were performed to determine the potential relationships between variables and prognostic outcomes.

Results: One hundred and eighty-five patients (144 men, 41 women) received CRYO for small HCC, including 59 patients with age <50 years, 105 patients with age between 50 and 65 years, and 21 patients with age >65 years. The three age groups showed significant differences in the terms of underlying chronic liver disease and the number of patients with minor postoperative complications. After propensity score matching, the younger and elderly groups showed significant differences in mean OS (P=0.008) and tumor progression (P=0.050). However, no significant differences were shown in mean progression-free survival (PFS) (P=0.303). The Cox multivariate analysis showed that the Child-Pugh grade (HR=3.1, P<0.001), albumin (HR=0.85, P=0.004) and total of bilirubin (HR=1, P=0.024) were the independent prognostic factor for mean OS.

Conclusion: Our propensity-score-matched study suggested that elderly patients with small HCC can achieve acceptable prognostic outcomes with PFS similar to those of younger patients with small HCC after treatment with CRYO, while Child-Pugh grade, bilirubin and serum albumin levels were associated with the prognosis of small HCCs.

KEYWORDS

(LTP) local tumor progression, (OS) overall survival, (TFS) tumor-free survival, (HCC) hepatocellular carcinoma, (MRI) magnetic resonance imaging, (AFP) α-fetoprotein, (MWA) microwave ablation, (RFA) radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is the third leading cause of malignancy-related deaths (1). HCC is common with increasing life expectancy and is expected to become more common in elderly patients over time. As consequence, the management of elderly HCC patients is now a global issue. Currently diagnostic techniques advances and the availability of screening for high-risk individuals, more and more patients with HCC are being detected at earlier stages, leading to access to radical treatment options, including hepatic resection, liver transplantation and ablation (2). Among them, ablative therapy, especially cryoablation (CRYO) and microwave ablation (MWA), has been considered an effective modality for the treatment of early- and very early-stage HCC (3–5). Compared with open surgery, these treatment modalities have the advantages of being minimally invasive, safe, with fewer complications and faster postoperative recovery.

Previous studies have found that some changes in liver structure and function occur in the elderly population (6–9). In clinical practice, elderly patients with HCC usually have worse liver function and a higher incidence of comorbidities (10). Therefore, the choice of treatment for these patients is often more cautious and the indications for surgery are more stringent. Currently, there are no clear guidelines or strategies to instruct the treatment protocols for elderly patients with small HCC. In particular, it is unclear whether CRYO performed on elderly patients can achieve similar clinical outcomes as younger patients. Therefore, we designed this study in order to clarify the efficacy of the elderly small HCC population after CRYO treatment, as well as to explore the impact of age on clinical outcome. We expect that the findings of this study will contribute to refining the indications for percutaneous ablation in the elderly population and provide an important reference for clinical decision making.

Materials and methods

Patients

This retrospective study was approved by the medical ethics committee of the Fifth Medical Center of Chinese PLA General Hospital, China. Written informed consent was obtained from each patient in the study. From July 2007 to June 2013, 185 patients with a clinical diagnosis of small HCC who were treated with percutaneous CRYO were included in this study (Figure 1). According to the Barcelona Clinic Liver Cancer (BCLC) System, small HCC is defined as very early or early stage HCC (11, 12). Inclusion criteria of this study were as follows: (1) small HCC confirmed by imaging or pathological examination; (2) ineligible for surgical resection or liver transplantation; without evidence of vascular invasion, bile duct invasion, or extrahepatic metastasis; (3) preoperative CT/MRI imaging scans, laboratory test records and survival information are available; and (4) CRYO was an initial treatment. The exclusion criteria are following: (1) recurrent small HCC; (2) with severe comorbidities that cannot endure treatment; (3) severe coagulation disturbance; (4) patients who met inclusion criteria but declined to participate in the study or follow up; (5) patients who preferred to receive surgical resection or liver transplantation treatment or other therapies.

Percutaneous argon-helium CA procedures

The argon-helium based EndoCare system (EndoCare, Irvine, CA, USA) was applied to perform CRYO (13–15). Various sizes of cryoprobes were used (2 or 3 mm in diameter). The area to be frozen included both the entire tumor area and at least 5-10 mm of paraneoplastic liver tissue outside the tumor area. After local anesthesia, the cryoprobe was inserted into the tumor by a percutaneous approach using CT guidance. The cryoprobe is advanced under guidance until it reaches the distal edge of the target lesion. A dual freeze-thaw cycle consists of 20 minutes of freezing, 10 minutes of thawing, and another 15 minutes of freezing. After removal of the probe, all tracts were packed through the intrathecal guide with Surgicel (Johnson & Johnson, Arlington, TX, USA) to control bleeding, and then the intrathecal guide was removed.

Follow-up

The follow-up protocol including routine physical examination, laboratory tests and prothrombin time, and contrast-enhanced imaging including CT or MRI. All patients were followed up every

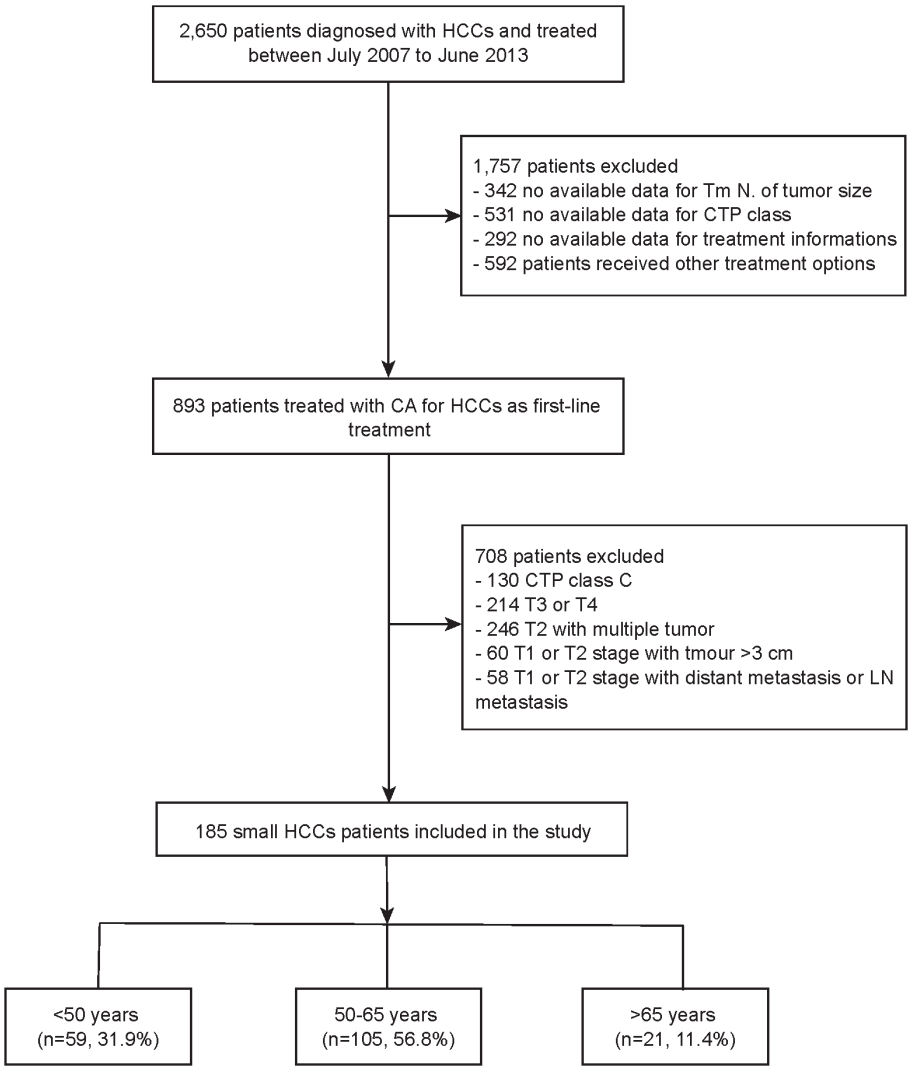

FIGURE 1
The flowchart of enrolled patients.

three months in the first year and twice a year thereafter to detect tumor recurrence.

Variable collection and definition

Demographic information, serologic biochemical test outcomes, alpha-fetoprotein (AFP) and types of underlying chronic liver disease were collected. Liver function was assessed by Child-Pugh grade. Physical condition was assessed by Eastern Cooperative Oncology Group (ECOG) score. The short-term outcomes included the number of patients with complete ablation, the number of patients with postoperative minor complications and major complications. Long-term outcomes included the number of deaths, the number of tumor-related deaths, the number of patients with tumor progression, the mean overall survival (OS) and progression-free survival (PFS). Complete ablation was defined as tumor tissue completely covered by the ablation area and there was no enhancement in the ablation area during the initial 1-month CT and MRI follow-up (13). Minor complications were defined as adverse events leading to minor consequences, including pain, fever, and bleeding from the needle tract. Major complications were defined as adverse events leading to serious consequences, including hepatic rupture and bleeding, spontaneous peritonitis, and death.

Statistical analysis

Patients were divided into three groups according to age distribution: group 1, <50 years, group 2, 50–65 years, and group 3, >65 years. To reduce the effect of bias and confounding variables, a 1:1 propensity score matching with a caliper of 0.05 was used to match

group 3 with the other groups. The continuous variables are expressed as the mean and standard deviation and the categorical variables are expressed as the frequency or percentage. To compare differences between groups, continuous variables were analyzed by the Mann-Whitney U test and Kruskal-Wallis test when non-normally distributed, and categorical variables were analyzed by the Chi-Square test or Fisher exact test as appropriate. OS and PFS were analyzed by the Kaplan-Meier (KM) method and compared by the log-rank test. The rate of LTP, distant recurrence, and OS was calculated using the Kaplan-Meier method. Univariate and multivariate Cox analyses were performed to determine the potential relationships between variables and prognostic outcomes. A two-sided P value <0.05 was considered statistically significant. Packages R software (http://www.R-project.org; The R Foundation) was used to perform all statistical analyses.

Results

Patients included and baseline characteristics

The detailed information of 185 patients with small HCC are summarized in Table 1. There are 144 men and 41 women, with a mean age of 53.8 ± 9.7 (range, 22-75). Of these patients, 166 patients (89.7%) were HBsAg (surface antigen of the hepatitis B virus) positive, 25 patients (13.5%) were anti-HCV (hepatitis C virus) positive, 6 patients (3.2%) were both HBsAg positive and anti HCV positive, and 2 patients (1.1%) for other reasons (alcoholic). Regarding liver function, 164 patients (88.6%) were Child–Pugh Class A and 21 patients (11.4%) were Child–Pugh B. The mean length of postoperative follow-up was 45.2 months.

TABLE 1 Baseline characteristics of included patients.

Variable	Group 1 (*n*=59)	Group 2 (*n*=105)	Group 3 (*n*=21)	*P* value
Age (years)	42.98 ± 5.87	56.78 ± 4.45	69.62 ± 3.11	<0.01
Sex (male)	45 (76.3%)	87 (82.9%)	15 (71.4%)	0.361
BMI				0.989
<18.5	6 (10.2%)	13 (12.4%)	2 (9.5%)	
18.5-24.9	42 (71.2%)	72 (68.6%)	16 (76.2%)	
>25	11 (18.6%)	20 (19.0%)	3 (14.3%)	
Hypertension	21 (35.6%)	45 (42.9%)	7 (33.3%)	0.547
Diabetes mellitus	5 (8.5%)	13 (12.4%)	3 (14.3%)	0.668
Cardiovascular disease	26 (44.1%)	71 (67.6%)	9 (42.9%)	<0.01
Respiratory disease	4 (6.8%)	16 (15.2%)	8 (38.1%)	<0.01
Cerebrovascular disease	1 (1.7%)	5 (4.8%)	3 (14.3%)	0.084
Tumor size (cm)	2.26 ± 0.68	2.13 ± 0.78	2.26 ± 0.82	0.513
AFP (mg/L)	454.36 ± 1033.52	224.90 ± 734.08	86.99 ± 139.05	0.386
Platelet count ($\times10^9$/L)	101.69 ± 67.92	105.04 ± 57.43	112.96 ± 46.40	0.342
Albumin (g/L)	36.46 ± 5.53	37.17 ± 5.49	37.29 ± 4.51	0.885
Total bilirubin (μmol/L)	19.23 ± 12.40	20.14 ± 17.05	20.01 ± 14.04	0.996
Underlying chronic liver disease				0.042
HBV infection	56 (94.9%)	91 (86.7%)	19 (90.5%)	
HCV infection	3 (5.1%)	15 (14.3%)	7 (33.3%)	
Other	1 (1.7%)	1 (1.0%)	0 (0.0%)	
Child-Pugh grade				0.495
A	51 (86.4%)	95 (90.5%)	18 (85.7%)	
B	8 (13.6%)	10 (9.5%)	3 (14.3%)	
ECOG score				0.863
0	0 (0.0%)	1 (1.0%)	0 (0.0%)	
1	54 (91.5%)	90 (85.7%)	18 (85.7%)	
2	5 (8.5%)	14 (13.3%)	3 (14.3%)	

BMI, Body mass index; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group.

Comparison of baseline characteristics

The number of patients included in the three groups was as follows: 59 patients (31.9%) in group 1, 105 patients (56.8%) in group 2, and 21 patients (11.4%) in group 3. Significant difference between groups was observed in the baseline variables of underlying chronic liver disease (P=0.042) (Table 1).

Comparison of prognosis outcomes before propensity score matching

The short-term and long-term outcomes in the three age groups are listed in the Table 2. With regard to the short-term outcomes, the complete ablation was obtained in 56 (94.9%), 90 (85.7%) and 19 (90.5%) patients in groups 1-3 (P=0.189), respectively. The patients who developed minor complications were 31 (52.5%), 33 (31.4%) and 6 (28.6%) (P=0.022), respectively. The patients who developed major complications were 1 (1.7%), 7 (6.7%) and 0 (0.0%) (P=0.304), respectively.

With regard to the long-term outcomes, the number of deaths in groups 1-3 was 6 (10.2%), 6 (5.7%) and 1 (4.8%) (P=0.585), respectively. The number of tumor-specific deaths in groups 1-3 was 1 (1.7%), 1 (1.0%) and 0 (0.0%) (P=0.1), respectively. The OS was 40.99 ± 31.67, 47.05 ± 30.49 and 47.73 ± 29.21 months in group 1-3 (P=0.303), respectively. The rates of progression were 42.4%, 50.5% and 42.9% in group 1-3 (P=0.560), respectively. The PFS was 22.06 ± 20.22, 23.15 ± 19.33 and 33.22 ± 29.30 months in group 1-3 (P=0.337), respectively. The KM curve of OS is shown in Figure 2 and the log rank test found no significant differences (P=0.84) among the age groups. The KM curve of PFS is shown in Figure 3 and the log rank test found no significant differences (P=0.069) among the age groups.

Comparison of prognosis outcomes after propensity score matching

To further investigate the effect of age on prognosis, we used the group 3 as the elderly group and the first two groups as the younger group and compared these two groups. To reduce the effect of bias and confounding variables, including sex, BMI, the size of the tumors, AFP, albumin, total bilirubin, underlying chronic liver disease, comorbid conditions, Child Pugh grade and ECOG score, the propensity score was used to match comparable patients to obtain the younger group for comparison. The median age of younger group was 51.9 ± 9.1 years. The baseline characteristics of the patients before and after matching are shown in Table 3. A comparison of short-term and long-term outcomes before and after matching is shown in Table 4.

With regard to the short-term outcomes, the number of complete ablations in group younger and older was 146 (89.0%) and 19 (90.5%) (P=1.000), respectively. The number of patients with minor complications was 64 (39.0%) and 6 (28.6%) (P=0.352), respectively. The number of patients with major complications was 8 (4.9%) and 0 (0.0%) (P=0.642), respectively. After matching, there was still no significant difference in the number of patients with complete ablation (P=1.000) and number of patients with minor complications (P=0.097).

With regard to the long-term outcomes, the number of deaths in group younger and older was 12 (7.3%) and 1 (4.8%) (P=1.000), respectively. The number of tumor-specific death was 7 (4.1%) and 0 (0.0%) (P=0.813), respectively. The OS was 44.9 ± 30.0 and 47.73 ± 29.21 months (P=0.689), respectively. The rates of progression were 47.6% and 42.9% (P=0.684), respectively. The PFS was 22.8 ± 19.6 and 33.22 ± 29.30 months (P=0.126), respectively. After matching, the OS was 77.6 ± 38.6 and 46.6 ± 28.8 months (P=0.008), respectively. The KM curve of OS is shown in Figure 4 and the log rank test found significant differences (P=0.010). The rates of progression were 68.4% and 36.8% (P=0.050), respectively. The PFS was 25.6 ± 25.5 and 35.0 ± 29.9 months (P=0.303), respectively. The KM curve of PFS is shown in Figure 5 and the log rank test found no significant differences (P=0.210) among the age groups.

Analysis of risk factors for prognosis outcomes

The univariate analysis revealed that the use of alcohol (HR=3.3, P=0.045), Child-Pugh grade (HR=8.5, P<0.001), platelet count

TABLE 2 Prognostic outcomes for groups 1–3.

Variable	Group 1 (*n*=59)	Group 2 (*n*=105)	Group 3 (*n*=21)	*P* value
Short-term outcomes				
Complete ablation	56 (94.9%)	90 (85.7%)	19 (90.5%)	0.189
Minor complications	31 (52.5%)	33 (31.4%)	6 (28.6%)	0.022
Major complications	1 (1.7%)	7 (6.7%)	0 (0.0%)	0.304
Long-term outcomes				
Death	6 (10.2%)	6 (5.7%)	1 (4.8%)	0.585
Tumor-specific death	1 (1.7%)	1 (1.0%)	0 (0.0%)	1
OS	40.99 ± 31.67	47.05 ± 30.49	47.73 ± 29.21	0.303
Tumor progression	25 (42.4%)	53 (50.5%)	9 (42.9%)	0.560
PFS	22.06 ± 20.22	23.15 ± 19.33	33.22 ± 29.30	0.337

OS overall survival, PFS progression-free survival.

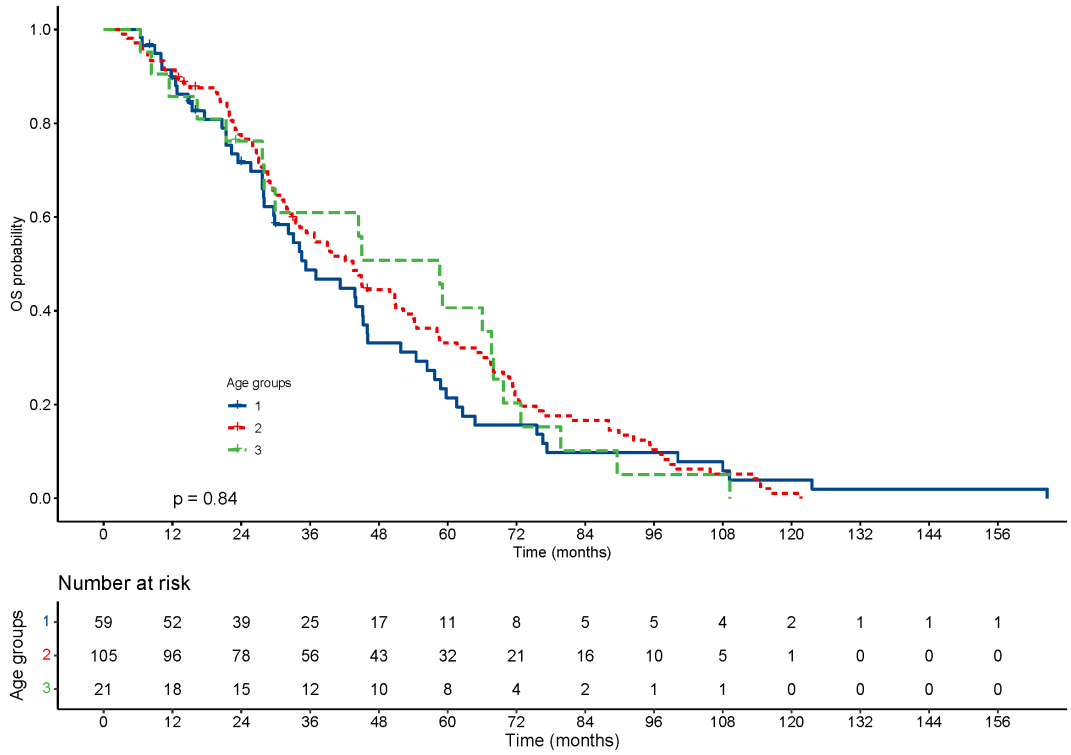

FIGURE 2
Kaplan–Meier curves for overall survival (OS) of patients with small hepatocellular carcinomas after cryoablation. The log-rank test showed no significant difference between the four groups (P=0.84).

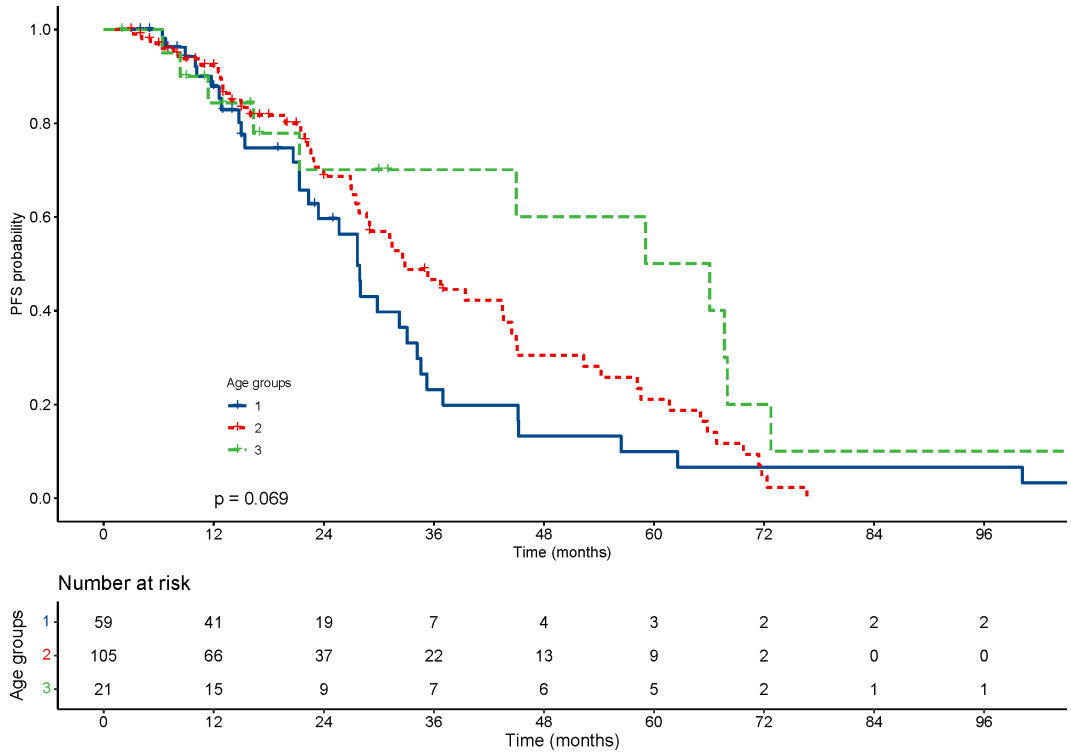

FIGURE 3
Kaplan–Meier curves for progression-free survival (PFS) of patients with small hepatocellular carcinomas after cryoablation. The log-rank test showed no significant difference between the four groups (P =0.069).

TABLE 3 Baseline characteristics of Group younger (≤65 years) and Group elderly (>65 years) before and after matching.

Variable	Younger (*n*=164)	Elderly (*n*=21)	*P* value	Younger (*n*=19)	Elderly (*n*=19)	*P* value
Age (years)	51.8 ± 8.3	69.6 ± 3.1	<0.001	51.9 ± 9.1	69.4 ± 3.0	<0.001
Sex (male)	129 (78.7%)	15 (71.4%)	0.637	16 (84.2%)	15 (78.9%)	1
BMI			0.933			0.864
<18.5	19 (11.6%)	2 (9.5%)		2 (10.5%)	2 (10.5%)	
18.5-24.9	114 (69.5%)	16 (76.2%)		13 (68.4%)	15 (78.9%)	
>25	31 (18.9%)	3 (14.3%)		4 (21.1%)	2 (10.5%)	
Hypertension	66 (40.2%)	7 (33.3%)	0.709	6 (31.6%)	6 (31.6%)	1
Diabetes mellitus	18 (11.0%)	3 (14.3%)	0.713	4 (21.1%)	3 (15.8%)	1
Cardiovascular disease	97 (40.2%)	9 (42.9%)	0.235	5 (26.3%)	9 (47.4%)	0.313
Respiratory disease	20 (12.2%)	8 (38.1%)	<0.01	8 (42.1%)	7 (36.8%)	1
Cerebrovascular disease	6 (3.7%)	3 (14.3%)	0.068	1 (5.3%)	3 (15.8%)	0.604
Tumor size (cm)	2.2 ± 0.7	2.3 ± 0.8	0.639	2.1 ± 0.9	2.3 ± 0.9	0.573
AFP (mg/L)	307.4 ± 858.0	87.0 ± 139.1	0.003	347.3 ± 716.6	83.9 ± 141.4	0.125
Platelet count ($\times10^9$/L)	103.8 ± 61.2	113.0 ± 46.4	0.511	82.9 ± 37.3	114.4 ± 45.3	0.025
Albumin (g/L)	36.9 ± 5.5	37.3 ± 4.5	0.767	36.7 ± 5.0	37.6 ± 4.5	0.588
Total bilirubin (μmol/L)	19.8 ± 15.5	20.0 ± 14.0	0.955	19.2 ± 1.7	18.9 ± 12.9	0.941
Underlying chronic liver disease			0.082			0.191
HBV infection	147 (89.6%)	19 (90.5%)		18 (94.7%)	17 (89.5%)	
HCV infection	18 (11.0%)	7 (33.3%)		1 (5.3%)	5 (26.3%)	
Other	2 (1.2%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Child-Pugh grade			0.74			1
A	146 (89.0%)	18 (85.7%)		17 (89.5%)	17 (89.5%)	
B	18 (11.0%)	3 (14.3%)		2 (10.5%)	2 (10.5%)	
ECOG score			0.725			0.105
0	1 (0.6%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
1	144 (87.8%)	18 (85.7%)		15 (78.9%)	18 (94.7%)	
2	19 (11.6%)	3 (14.3%)		4 (21.1%)	1 (5.3%)	

BMI, Body mass index; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group.

(HR=0.98, P=0.034), albumin (HR=0.83, P<0.001) and total bilirubin (HR=1, P=0.017) were predictors associated with overall survival. The multivariate analysis showed that the Child-Pugh grade (HR=3.1, P<0.001), albumin (HR=0.85, P=0.004) and TBIL (HR=1, P=0.024) were the independent prognostic factor (Table 5).

Discussion

Numerous age-related changes in hepatic structure and function have been described, including changes in the size of hepatocytes and changes in the mitochondria and endoplasmic reticulum inside the hepatocytes. Some animal experiments have also confirmed the declined function and regeneration rate of the liver in aged animals. These age-related changes have important clinical implications with regard to treatment options for small hepatocellular carcinoma. However, some studies suggest that age should not be a determining factor in such clinical decisions. Some elderly patients exhibit decreased adaptive hepatic responsiveness, characterized by decreased hepatic clearance of drugs and increased rates of adverse drug reactions, while maintaining liver function within the normal range. In the present study, the OS after CA decreased with ageing, with a mean of 77.6 ± 38.6 months in the younger patient group (under 65 years) and 46.6 ± 28.8 months in the elderly patient group (over 65 years). However, the PFS after CA was not significantly associated with age.

The findings of this study may have implications for clinical practice. Clinicians are concerned about referring elderly patients with small HCC for surgery because of minimal benefit from open surgery at advanced age. In this clinical scenario, minimally invasive treatment modalities may usually be considered. The study by Zhang et al. (16) found that elderly patients with HCC, even if associated with more comorbidities, may achieve similar prognostic outcomes

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TABLE 4 Prognostic outcomes before and after matching.

Variable	Younger (*n*=164)	Elderly (*n*=21)	*P* value	Younger (*n*=19)	Elderly (*n*=19)	*P* value
Short-term outcomes						
Complete ablation	146 (89.0%)	19 (90.5%)	1.000	18 (94.7%)	17 (89.5%)	1.000
Minor complications	64 (39.0%)	6 (28.6%)	0.352	10 (52.6%)	5 (26.3%)	0.097
Major complications	8 (4.9%)	0 (0.0%)	0.642	0 (0.0%)	0 (0.0%)	NA
Long-term outcomes						
Death	12 (7.3%)	1 (4.8%)	1.000	1 (5.3%)	1 (5.3%)	1.000
Tumor-specific death	7 (4.1%)	0 (0.0%)	0.813	0 (0.0%)	0 (0.0%)	NA
OS	44.9 ± 30.0	47.7 ± 29.2	0.689	77.6 ± 38.6	46.6 ± 28.8	0.008
Tumor progression	78 (47.6%)	9 (42.9%)	0.684	13 (68.4%)	7 (36.8%)	0.050
PFS	22.8 ± 19.6	33.2 ± 29.3	0.126	25.6 ± 25.5	35.0 ± 29.9	0.303

OS, overall survival; PFS, progression-free survival; NA, not available.

after microwave ablation (MWA) as younger patients. However, similar studies have not been performed extensively in elderly patients undergoing cryoablation. Cryoablation is an extremely effective treatment modality, more research on the cost-effectiveness of cryoablation needs to be conducted to gain more insight into the most suitable surgical population.

In the current study, we compared the baseline characteristics and prognosis of patients in different age groups and found some differences between these groups. We observed significant differences in the distribution of hepatitis virus types and tumor-related mortality. Among them, with increasing age, the probability of liver cancer is higher in HCV-infected patients, but lower in HBV-infected patients, which is similar to the results of other studies (17, 18). The reason behind this phenomenon may be due to the older age of HCV-infected patients than HBV-infected patients. We consider that elderly patients are a particular population with unique characteristics. Therefore, after matching patients in the older and younger groups by propensity score matching, we found that patients in the older group had shorter overall survival and lower rates of tumor progression. In addition, there were no significant differences

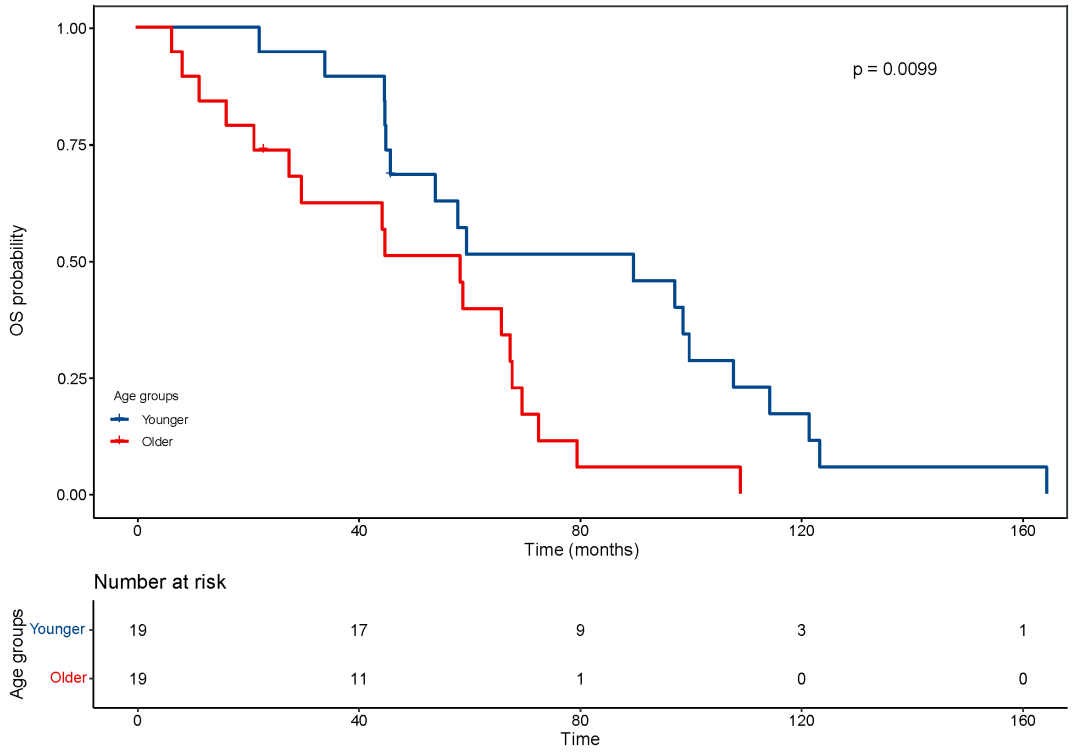

FIGURE 4
Kaplan–Meier curves for overall survival (OS) of patients with small hepatocellular carcinomas after cryoablation. The log-rank test showed significant difference between the elderly and young groups (P <0.01).

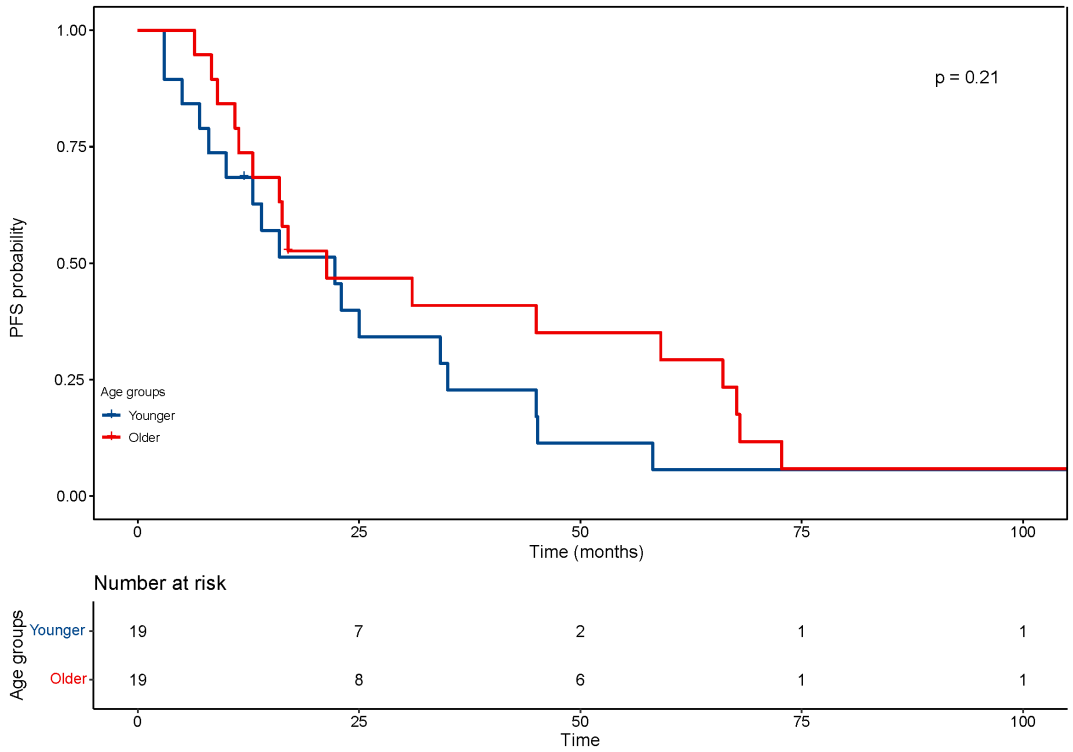

FIGURE 5
Kaplan–Meier curves for progression-free survival (PFS) of patients with small hepatocellular carcinomas after cryoablation. The log-rank test showed no significant difference between the four groups (P =0.21).

TABLE 5 Univariate and multivariate analyses of factors associated with overall survival (OS).

	Univariate				Multivariate			
		95% CI				95% CI		
	HR	Lower	Upper	*P* value	HR	Lower	Upper	*P* value
Age, years	0.97	0.92	1	0.300				
Sex, male	0.29	0.038	2.2	0.230				
BMI	0.99	0.37	2.7	0.980				
Family history of HCV	1.3	0.3	6.1	0.700				
Family history of HBV	1.1	0.62	2	0.710				
Alcohol	3.3	1	11	0.045				
Smoke	1.6	0.5	4.8	0.450				
Diabetes	0.69	0.09	5.3	0.720				
Tumor size, cm	0.82	0.39	1.8	0.620				
Child-Pugh grade	8.5	3	24	<0.001	3.1	1.5	19	<0.001
ECOG score	1	0.31	3.3	0.990				
AFP, mg/L	1	1	1	0.550				
Platelet count ($\times10^9$/L)	0.98	0.97	1	0.034				
Albumin, g/L	0.83	0.75	0.91	<0.001	0.85	0.77	0.95	0.004
Total bilirubin, μmol/L	1	1	1	0.017	1	1	1.1	0.024

BMI, Body mass index; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group.

in short-term postoperative outcomes and PFS between the two age groups after matching, indicating that the safety and progression-free survival of CA did not vary with age, further implying that the survival outcomes of the older group were not worse than those of the younger patients, as shown in Table 4. These findings suggest that older patients can benefit equally from CA compared to younger patients with similar liver function and tumor burden.

Over the decades, many biomarkers have been shown to be effective predictors of liver tumor recurrence and prognosis, including Child-Pugh grade, alpha-fetoprotein (AFP), alanine aminotransferase (ALT), albumin (ALB), and TBIL (19–21). Among them, the Child-Pugh and Model for End-Stage Liver Disease (MELD) scores are well-known prognostic tools for liver function and have been widely used in the prognosis of patients with liver disease. The Child-Pugh grade is used as a frequently used tool to assess liver function and predict postoperative outcomes, including subjective variables such as ascites, TBIL and encephalopathy. Several previous studies have found a strong sensitivity of the Child-Pugh grade in predicting the prognosis of various treatment modalities for HCC. Zhang et al. showed that the Child-Pugh grade can be used as an independent risk factor to predict the prognosis of microwave ablation procedures for HCC. Huang et al. found that the Child-Pugh grade performed better in predicting the prognosis of HCC patients undergoing hepatectomy and was more accurate than the ALBI score. In the present study, Child-Pugh grade and TBIL were shown by Cox regression analysis to be independent risk factors for predicting prognosis in patients with small HCC, and these results were similar to those of previous studies.

The Glasgow prognostic score, which includes serum albumin levels and C-reactive protein, is a powerful prognostic assessment tool for a variety of malignancies (22, 23). Among them, serum albumin levels have been shown to play an essential role in the prognosis of HCC. Several researchers found that albumin gene expression levels and mRNA levels were significantly lower in liver tumor tissues compared to normal human liver tissues (24, 25). A study by Bağırsakçı et al. (26) showed that lower albumin levels were associated with larger tumor volumes and higher AFP levels. Also, they found that the adding of albumin to HCC cell lines significantly inhibited the growth of tumor cells. Similar to these studies, in the current study, we also found that higher serum albumin levels were a protective factor for the prognosis of small HCC. The results of the present study may contribute to further clarification of HCC-related prognostic parameters.

There are some limitations to this study. First, the most significant limitation of this study was the relatively small number of patients >65 years old included, which may have diminished the statistical power of the results. Future studies need to further expand the cohort of patients of advanced age to elicit more reliable results. Second, this was a single-center study with a relatively limited sample size included. This may have affected the results of the study. Therefore, the sample should be further expanded in future studies to validate the findings of this study. Third, the applicable population for the results of this study needs further discussion. In the Chinese population, most HCC are caused by hepatitis B virus, however, in the European and American populations, most HCC are caused by hepatitis C virus and alcoholic. Therefore, more multicenter and multiethnic studies need to be conducted to validate the findings of this study. Fourth, the efficacy of CA is related to the surgical technique. Surgical techniques of different physicians among different centers may result in inconsistent prognostic outcomes.

In conclusion, this study shows that the elderly population can achieve acceptable prognostic outcomes with PFS times similar to those of younger people after treatment with CA. Also, we found that Child-Pugh grade and TBIL were independent risk factors for poor prognosis, while higher serum albumin levels was a protective factor. Our findings further demonstrate the suitability of this type of surgery for CA in elderly patients and provide a clinical reference for the indication of surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the medical ethics committee of the Fifth Medical Center of Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Concept and design: YY and ZZ. Data analysis: HZ, MX, JS, HK, XG, WZ, XC, BY, YC, ZD, JH. Writing and critical analysis: All. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Alberto Puccini,
Ospedale Policlinico San Martino IRCCS, Italy

REVIEWED BY
Rongxing Zhou,
Sichuan University, China
Vikram Chaudhari,
Tata Memorial Hospital, India

*Correspondenc: Xiao-Qing Jiang
jxq1225@sina.com
Qing-Bao Cheng
13916309500@126.com

†These authors have contributed equally to this work and share first authorship

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Development and validation of a nomogram to predict overall survival in patients with incidental gallbladder cancer: A retrospective cohort study

Zhi-Hua Xie[1†], Xuebing Shi[1†], Ming-Qi Liu[1†], Jinghan Wang[2], Yong Yu[1], Ji-Xiang Zhang[1], Kai-Jian Chu[1], Wei Li[1], Rui-Liang Ge[1], Qing-Bao Cheng[1*] and Xiao-Qing Jiang[1*]

[1]Department I of Biliary Tract Surgery, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai, China, [2]Department of Hepatopancreatobiliary Surgery, East Hospital, Tongji University, Shanghai, China

Objective: The aim of this study was to develop and validate a nomogram to predict the overall survival of incidental gallbladder cancer.

Methods: A total of 383 eligible patients with incidental gallbladder cancer diagnosed in Shanghai Eastern Hepatobiliary Surgery Hospital from 2011 to 2021 were retrospectively included. They were randomly divided into a training cohort (70%) and a validation cohort (30%). Univariate and multivariate analyses and the Akaike information criterion were used to identify variables independently associated with overall survival. A Cox proportional hazards model was used to construct the nomogram. The C-index, area under time-dependent receiver operating characteristic curves and calibration curves were used to evaluate the discrimination and calibration of the nomogram.

Results: T stage, N metastasis, peritoneal metastasis, reresection and histology were independent prognostic factors for overall survival. Based on these predictors, a nomogram was successfully established. The C-index of the nomogram in the training cohort and validation cohort was 0.76 and 0.814, respectively. The AUCs of the nomogram in the training cohort were 0.8, 0.819 and 0.815 for predicting OS at 1, 3 and 5 years, respectively, while the AUCs of the nomogram in the validation cohort were 0.846, 0.845 and 0.902 for predicting OS at 1, 3 and 5 years, respectively. Compared with the 8th AJCC staging system, the AUCs of the nomogram in the present study showed a better discriminative ability. Calibration curves for the training and validation cohorts showed excellent agreement between the predicted and observed outcomes at 1, 3 and 5 years.

Conclusions: The nomogram in this study showed excellent discrimination and calibration in predicting overall survival in patients with incidental gallbladder cancer. It is useful for physicians to obtain accurate long-term survival information and to help them make optimal treatment and follow-up decisions.

KEYWORDS

gallbladder cancer, re-resection, nomogram, overall survival, incidental gallbladder cancer

1 Introduction

Gallbladder cancer (GBC) is a rare malignancy with a documented incidence of 1.13 per 100,000 (1). Most patients are diagnosed with advanced incurable disease with a poor prognosis. The 5-year overall survival (OS) for stage III was 22.1% to 25.7% and 6.7% to 15.7% for stage IV patients (2). Radical resection is the only potential cure for GBC patients, especially those in early stages, who are most frequently diagnosed incidentally. In particular, with the widespread adoption of laparoscopic cholecystectomy, the number of incidentally gallbladder cancers (IGBCs) discovered after cholecystectomy for presumed benign disease has increased dramatically, accounting for 1.6% of all cholecystectomies (3). Due to the predisposition of port-site metastasis, peritoneal metastasis and the possibility of tumor residual in the liver bed and/or regional lymph nodes after initial cholecystectomy, the optimal management of IGBCs after the index cholecystectomy is a challenge which has attracted physicians' attention.

Although the extent and timing of reresection for IGBC remain controversial, reoperation has been recommended because of improved survival in retrospective studies. The rationale behind reresection is not only to remove any residual disease but also to restage the disease accurately, which may be instrumental in achieving tumor-free margins, guiding adjuvant therapy and predicting prognosis (4–6). However, the existing survival prediction models of GBC do not take its specific characteristics (such as reresection and time to reoperation) into account due to its low incidence (7–13), and may not be able to provide accurate survival predictions for patients with IGBC and reduce the prognostic value of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system model. Therefore, in this special group of patients, it is necessary to identify independent prognostic factors associated with IGBC survival and develop an appropriate model to accurately predict the survival rate of IGBC.

Recently, user-friendly and intuitive nomograms that can accurately predict overall survival have been widely used to evaluate the prognosis of various cancers. In this study, univariate and multivariate analyses were used to explore the independent prognostic factors of IGBC based on the clinicopathological data collected from our center in the past decade. Next, a nomogram was established to predict OS, and the accuracy and precision of the nomogram in the training and validation sets were evaluated by receiver operating characteristic (ROC) curves and calibration curves, respectively.

2 Materials and methods

2.1 Patient selection

This study was approved by the institutional Review Board of our Ethics Committee, and informed patient consent was obtained (No. EHBHKY2022-K-025). The patients who underwent index cholecystectomy and were diagnosed with IGBC in Eastern Hepatobiliary Surgery Hospital from 2011 to 2021 and those who were first diagnosed with IGBC in other hospitals and underwent reresection for curable purposes in our hospital during the period were retrospectively analyzed. All enrolled cases were randomly divided into two datasets: 70% of eligible cases were allocated to the training cohort (n=269), and 30% were allocated to the validation cohort (n=114). The inclusion criteria for both cohorts were all patients diagnosed with incidental gallbladder cancer, defined as patients with no preoperative suspicion of GBC but pathologically confirmed gallbladder malignant tumor after cholecystectomy. Patients who were under the age of 18 years at diagnosis or lacked follow-up information were excluded. Clinical information such as sex, age at diagnosis, histology type, T stage, N metastasis, peritoneal metastasis, etc., were reviewed from medical records. The cutoff value of the time to reoperation was defined as the median time (19 days). The histological classification was adenocarcinoma or nonadenocarcinoma (adenosquamous or squamous). N metastasis was described as either negative or positive lymph node status. M metastasis was described as either negative or positive distant metastasis. Resection margin R was described as either negative (R0) or positive (R1/R2). Overall survival was chosen as the endpoint of interest, with dates calculated from the time of first surgery to death from any cause or the last follow-up on January 1, 2022.

2.2 Statistical analysis

Descriptive statistics were used to summarize all clinical features. χ^2 or Fisher's exact tests were performed to assess the distribution of basic categorical variables of patients in the training and validation cohorts, as appropriate. Potential prognostic variables with p values <0.1 identified in univariable Cox analyses were further selected and included in multivariable Cox regression analyses. Stepwise backward model selection was performed based on Akaike information criterion (AIC) values. Variables with two-sided p values <0.05 were considered as statistically significant and were identified as independent prognostic factors to construct a nomogram of the prediction model. In the training and validation cohorts, the nomogram was validated both internally and externally with 500-bootstrap resampling.

Discrimination and calibration were used to evaluate the predicted OS performance of the nomogram. Harrell's concordance index (C-index) was calculated to measure the difference between the observed outcomes and the nomogram predictions on a scale of 0.5 to 1.0, where 0.5 indicated no discrimination at all and 1.0 indicated a perfect fit. Calibration curves were visualized to compare the predicted and observed probabilities of OS at 1, 3 and 5 years. Furthermore, time-dependent ROC curves were generated to compare the power of the nomogram model with the 8th edition of the AJCC TNM staging system model. Missing data were completed with multiple imputation using the 'mice' package with default values. Statistical analyses were performed using version R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). The related R packages 'rms', 'foreign', 'VIM', 'epiDisplay', 'dplyr', 'mice', 'survival', 'survivalROC', 'forestplot', and 'caret' were applied to create and evaluate the nomogram. This study was designed according to the Transparent Reporting of a multivariable

prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.

3 Results

3.1 Clinical characteristics

A total of 383 patients with incidental gallbladder cancer who met the inclusion criteria were identified from 2011 to 2021. They were randomly divided into the training cohort (n=269, 70%) and validation cohort (n=114, 30%). All patients underwent surgical resection, of whom approximately 84.1% underwent reresection. The median follow-up was 31.3 months, with a range of 1.3 to 136 months. Detailed baseline characteristics of patients in each cohort are shown in Table 1. Approximately 64% of the cases were female, and 31.6% were male. There were slightly more patients under the age of 60 than those over the age of 60 (51.4% *vs.* 48.6%). Most of the patients had T2-T3 stages (315 cases, 82.2%) and adenocarcinomas (340 cases, 88.8%). More importantly, in these 383 patients, upon reresection, 9.7% developed distant metastases, 19.3% developed lymph node metastases, and 6.3% developed peritoneal metastases. Among the 383 cases, 141 (36.8%) had chronic disease. In addition, the median time to reoperation was 19 [InterQuartile Range (IQR), 12-26.5] days, and a total of 182 (47.5%) patients underwent reoperation within 19 days from their initial cholecystectomy.

3.2 Identification of prognostic factors

To identify prognostic factors associated with OS before constructing a nomogram model, we employed univariate and

TABLE 1 Characteristics of incidental gallbladder cancer patients in the Training and Validation set.

Characteristics	Training set	Validation set	Total	statistic	*P*
	269 (%)	114 (%)	383 (%)		
sex				$\chi2$= 1.4	0.237
female	167 (62.1)	78 (68.4)	245 (64)		
male	102 (37.9)	36 (31.6)	138 (36)		
age60				$\chi2$ = 0.09	0.761
<60year	137 (50.9)	60 (52.6)	197 (51.4)		
>=60year	132 (49.1)	54 (47.4)	186 (48.6)		
T stage				$\chi2$ = 1.77	0.777
T1	24 (8.9)	8 (7)	32 (8.4)		
T2	103 (38.3)	50 (43.9)	153 (39.9)		
T3	118 (43.9)	44 (38.6)	162 (42.3)		
T4	11 (4.1)	5 (4.4)	16 (4.2)		
NA	13 (4.8)	7 (6.1)	20 (5.2)		
M metastasis				$\chi2$ = 1.28	0.528
No	234 (87)	95 (83.3)	329 (85.9)		
Yes	23 (8.6)	14 (12.3)	37 (9.7)		
NA	12 (4.5)	5 (4.4)	17 (4.4)		
N metastasis				$\chi2$ = 1.94	0.379
No	209 (77.7)	81 (71.1)	290 (75.7)		
Yes	48 (17.8)	26 (22.8)	74 (19.3)		
NA	12 (4.5)	7 (6.1)	19 (5)		
TNM stage				$\chi2$= 2.12	0.713
I	23 (8.6)	8 (7)	31 (8.1)		
II	88 (32.7)	38 (33.3)	126 (32.9)		
III	114 (42.4)	43 (37.7)	157 (41)		
IV	34 (12.6)	20 (17.5)	54 (14.1)		

(Continued)

TABLE 1 Continued

Characteristics	Training set	Validation set	Total	statistic	*P*
	269 (%)	114 (%)	383 (%)		
NA	10 (3.7)	5 (4.4)	15 (3.9)		
Peritoneal metastasis				Fisher's	0.544
No	248 (92.2)	108 (94.7)	356 (93)		
Yes	19 (7.1)	5 (4.4)	24 (6.3)		
NA	2 (0.7)	1 (0.9)	3 (0.8)		
Lymphatic invasion				$\chi2$= 1.26	0.533
No	247 (91.8)	101 (88.6)	348 (90.9)		
Yes	10 (3.7)	7 (6.1)	17 (4.4)		
NA	12 (4.5)	6 (5.3)	18 (4.7)		
Perineural invasion				$\chi2$= 0.44	0.802
No	228 (84.8)	98 (86)	326 (85.1)		
Yes	29 (10.8)	10 (8.8)	39 (10.2)		
NA	12 (4.5)	6 (5.3)	18 (4.7)		
Vascular invasion				$\chi2$= 0.98	0.612
No	250 (92.9)	103 (90.4)	353 (92.2)		
Yes	7 (2.6)	5 (4.4)	12 (3.1)		
NA	12 (4.5)	6 (5.3)	18 (4.7)		
Resection margin R				Fisher's	0.399
negative	205 (76.2)	87 (76.3)	292 (76.2)		
positive	64 (23.8)	26 (22.8)	90 (23.5)		
NA	0 (0)	1 (0.9)	1 (0.3)		
Chronic disease				$\chi2$ = 0.21	0.648
No	168 (62.5)	74 (64.9)	242 (63.2)		
Yes	101 (37.5)	40 (35.1)	141 (36.8)		
Time to reoperation				$\chi2$= 0.03	0.853
<19d	127 (47.2)	55 (48.2)	182 (47.5)		
>=19d	142 (52.8)	59 (51.8)	201 (52.5)		
Re-resection				$\chi2$ = 0.07	0.797
No	42 (15.6)	19 (16.7)	61 (15.9)		
Yes	227 (84.4)	95 (83.3)	322 (84.1)		
Histology				$\chi2$= 1.3	0.523
Ade	242 (90)	98 (86)	340 (88.8)		
Nonade	8 (3)	5 (4.4)	13 (3.4)		
NA	19 (7.1)	11 (9.6)	30 (7.8)		

NA, not available; N metastasis, lymph node metastasis; M metastasis, distant metastasis; Ade, adenocarcinoma; Nonade, Noadenocarcinoma.

multivariate Cox regression analyses. Table 2 and Figure 1 show the detailed results of the univariate and multivariate analyses in the training cohort. Univariate analysis found that histology, M metastasis, N metastasis, perineural invasion, peritoneal metastasis, resection margin R, reresection, T stage, TNM stage and vascular invasion were associated with OS. Variables with *P values* <0.1 were considered as statistically significant. Subsequently, these ten meaningful variables were put into a multivariate Cox regression model using a backward stepwise method. Based on multivariate analysis, five variables (histology, N metastasis, peritoneal metastasis,

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TABLE 2 Univariable and multivariable Cox analyses of OS in patients with IGBC.

Variable	Univariate analysis			Multivariate analysis			
	HR	95% CI	P	HR	95% CI	β coef	P
Age60 (>=60year vs <60year)	1.03	0.7-1.52	0.864				
Chronic disease (Yes vs No)	0.76	0.5-1.14	0.187				
Histology (Nonade vs Ade)	2.52	1.17-5.45	0.018	2.3989	1.0919-5.2701	0.8750	0.02933 *
Time to reoperation (>1=19 vs <19)	0.8	0.54-1.17	0.253				
Lymphatic invasion (Yes vs No)	1.81	0.79-4.13	0.161				
M stage (Yes vs No)	3.58	2.13-6.01	0				
N metastasis (Yes vs No)	2.67	1.75-4.06	0	1.6627	1.0667-2.5919	0.5085	0.02477 *
Perineural invasion (Yes vs No)	1.71	0.97-3	0.063				
Peritoneal metastasis (Yes vs No)	3.54	2.06-6.06	0	2.3475	1.3308-4.1411	0.8534	0.00321 **
Resection margin R (Yes vs No)	3.35	2.26-4.96	0				
Re-resection (Yes vs No)	0.42	0.27-0.66	0	0.5195	0.3327-0.8112	-0.6549	0.00397 **
Sex (Male vs Female)	0.82	0.55-1.23	0.34				
T stage (IV vs III vs II vs I)	3.04	2.27-4.06	0	2.8838	2.1210-3.9209	1.0591	1.41e-11 ***
TNM stage (IV vs III vs II vs I)	2.98	2.3-3.88	0				
Vascular invasion (Yes vs No)	2.36	0.96-5.81	0.061				

OS, overall survival; IGBC, incidentally gallbladder cancer; Ade, adenocarcinoma; Nonade, Noadenocarcinoma.

reresection and T stage) were finally considered as independent prognostic factors with a *P* value <0.05 and a minimum AIC value of 1001.06.

3.3 Construction of the prognostic nomogram

Next, we successfully developed a nomogram model to predict OS at 1, 3, and 5 years based on the above five identified independent variables, as shown in Figure 2. According to the total subscale at the bottom, the probabilities of 1-, 3-, and 5-year OS were simply calculated from the sum of the scores for each individual variable. Harrell's C-index, time-dependent ROC curves (Figure 3) and calibration curves (Figure 4) were used to evaluate the established nomogram model. The C-index value of the nomogram was 0.76 [95% confidence interval (CI), 0.72-0.80] in the training cohort and 0.814 (95% CI, 0.76-0.87) in the validation cohort. Time-dependent ROC curves were used to compare the sensitivity and specificity between the predictive model and the TNM staging model. The areas under the curve (AUCs) of the nomogram for predicting OS at 1, 3, and 5 years were 0.8, 0.819 and 0.815 in the training cohort and 0.846, 0.845 and 0.902 in the validation cohort, respectively. Meanwhile, the 1-, 3- and 5-year AUC values of the TNM staging model were 0.722, 0.781 and 0.785 in the training cohort and 0.777, 0.822 and 0.874 in the validation cohort, respectively. As shown in Figure 3, in the training and validation cohorts of 1-, 3- and 5-year OS, the nomogram model showed better discriminative power and larger AUCs than the TNM staging model, illustrating that the nomogram model exhibited a more powerful discrimination. Meanwhile, calibration curves illustrating the relationship between predicted and actual OS probabilities were tested with 500 bootstrap resamples in both the training and validation cohorts. Calibration plots showed that OS prediction at 1, 3, and 5 years for both cohorts was in excellent agreement with actual observations. Taken together, the nomogram model demonstrated good discriminative and calibration power for predicting 1-, 3-, and 5-year OS in IGBC.

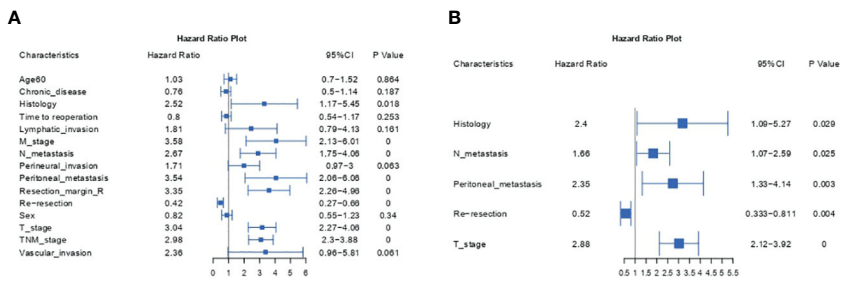

FIGURE 1
Forest plots of the univariate **(A)** and multivariate **(B)** Cox analyses.

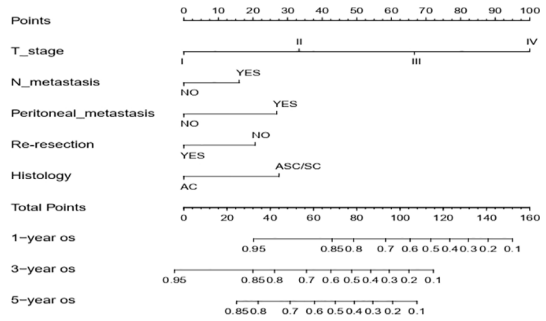

FIGURE 2
Nomogram for estimating the 1-, 3-, 5-year OS of IGBC patients. N metastasis, lymph node metastasis; AC, adenocarcinoma; ASC/SC, adenosquamous or squamous; OS, overall survival.

4 Discussion

Gallbladder cancer is an aggressive disease with a dismal prognosis. It is usually occult onset with an asymptomatic course that is not easily discovered in the early stages before operation. Most incidental gallbladder cancers were occasionally diagnosed after cholecystectomy, and a few were discovered during surgery. In recent decades, with the rapid increase in the number of patients undergoing laparoscopic cholecystectomy, the gradual increase in the incidence of IGBC is of concern. However, existing models and the latest AJCC TNM staging system for predicting survival in GBC that do not specifically consider IGBC may not be applicable to IGBC (7–14). Due to its user-friendly graphical interface and the integration of multiple easily accessible variables, the nomogram has been increasingly popular and widely used for personalized cancer prediction of various cancers. In this study, we first developed a nomogram model to predict survival for IGBC. Based on univariate and multivariate analyses, we identified five factors (T stage, N metastasis, peritoneal metastasis, reresection, histology) that were independently associated with overall survival.

T stage in our study was one of the top five independent prognostic factors that has also been identified in previous studies of IGBC (6, 15–17). Residual disease was considered as one of the most important characteristics of IGBC; in statistics, approximately 35% ~ 50.8% of patients had residual disease (RD) (4, 18), and T stage was closely associated with residual disease and proved to be an

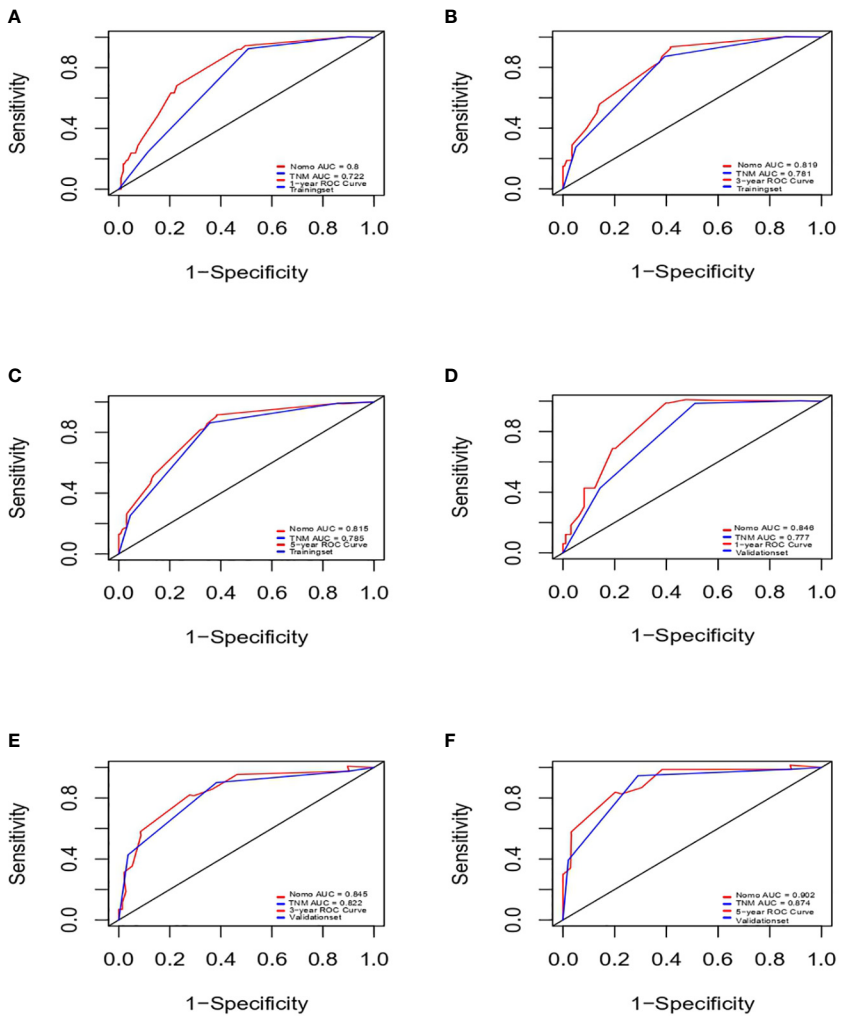

FIGURE 3
ROCs of IGBC for predicting OS at 1-, 3-, 5-year in the training **(A–C)** and validation set **(D–F)**, respectively. ROC, receiver operating characteristic; AUC, area under the curve; IGBC, incidentally gallbladder cancer; OS, overall survival.

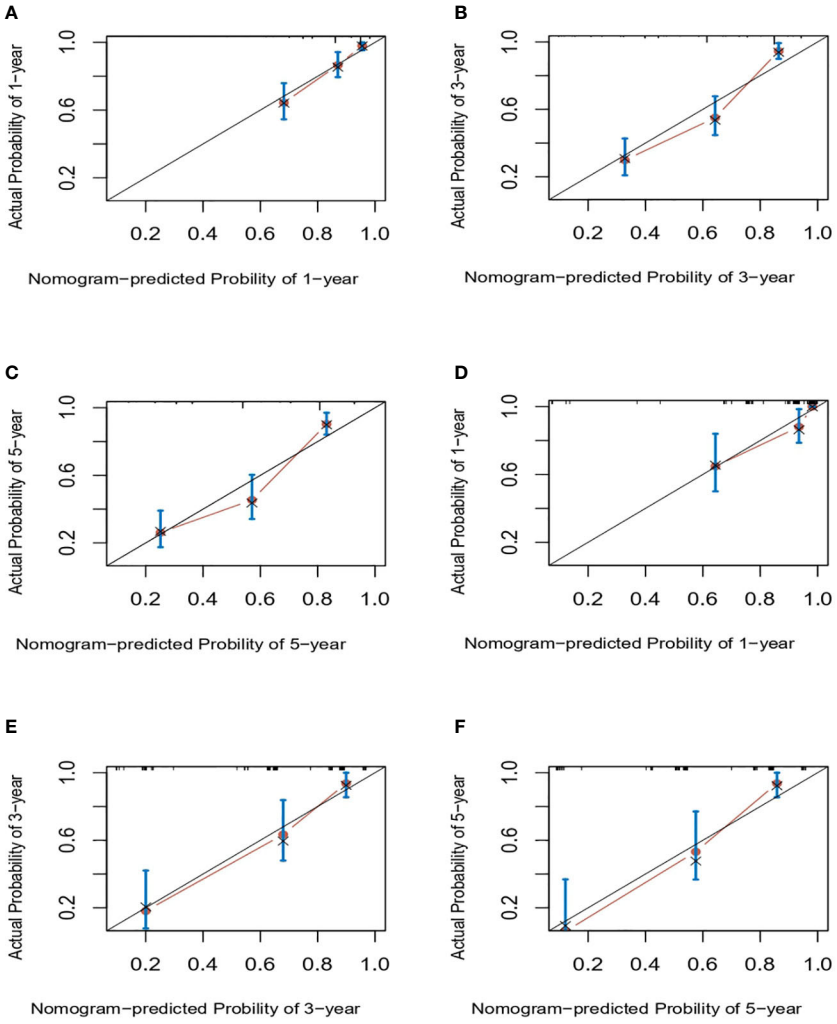

FIGURE 4
Calibration curves for predicting IGBC OS at 1-, 3-, 5-year in the training **(A–C)** and validation set **(C–E)**, respectively. IGBC, incidentally gallbladder cancer; OS, overall survival.

excellent predictor of residual disease in IGBC[18]. It was reported that approximately 20% of T1b, 23.8% of T2, and 71.7% of T3 of IGBC patients had accompanying RD (19). Evidently, R0 resection represents the strongest long-term prognostic factor and chance for cure. To remove microscopic or macroscopic RD, reoperation is recommended for T1b or higher IGBC by international guidelines (14). Consistent with previous studies, reresection is beneficial and associated with improved survival for patients with IGBC (4–6). Interestingly, resection margin status in our cohort did not show significant differences in prognosis for patients with IGBC after reoperation, which was also observed in the study of Vega and colleagues (20). However, the opposite conclusion can also be drawn from the work of de Savornin Lohman (4). The paradoxical results aroused our attention. Despite the improved survival observed in the reresection group, patients with RD have been shown to have shorter survival times than those without RD (4, 19). It is now evident that patients without residual disease or with disseminated disease cannot benefit from reoperation. Ramos' group (18) showed that only the patients with local RD that isolated nondiscontinuous involvement of the vesicular bed or the cystic stump were found to have acquired more benefit from reoperation compared with regional or distant RD. Similarly, the conclusion that reresection may be beneficial solely for patients with microscopic RD undetected by the pathologist was made by the de Savornin Lohman group (4). They perceived that the tumor may have already progressed beyond potential curation when macroscopic RD was found. In this regard, we presume that the difference in predictive prognosis efficacy of resection margin status may be due to the varying proportion of patients who can potentially benefit from reresection. Consequently, the survival benefit of reoperation for T1b IGBC remains controversial (21, 22). The survival benefit of reoperation for T2/T3 IGBC patients has reached an expert consensus (6, 22).

Additionally, peritoneal metastasis occurred frequently in IGBC, mainly due to bile spillage of the gallbladder during initial cholecystectomy, particularly in minimally invasive approaches on various conditions. It was an important factor for IGBC patients in

losing the chance of radical reoperation. Statistically, approximately 7-7.6% of patients with peritoneal metastasis were found to have reoperation (23, 24), which was similar to our results (6.3% of patients with peritoneal metastases during reoperation). Evidently, the poor prognosis association with peritoneal metastasis has also been demonstrated in multiple abdominal cancers, such as colorectal, gastric and liver cancers (25–27).

In addition, adenosquamous or squamous cell carcinoma represents a minority (2%) histological type of gallbladder cancer. Studies have shown that it is commonly larger and more aggressive than adenocarcinoma, with a significantly shorter median overall survival than adenocarcinoma, and is an independent prognostic factor for GBC (28, 29), which was similar to and supported our results.

In the present study, the proposed nomogram, which incorporated 5 comprehensive variables (including T stage, N metastasis, peritoneal metastasis, reresection and histology), performed well, as supported by the C index values of 0.76 and 0.814 in the training and validation cohorts, respectively, and the calibration curves showed excellent agreement between predicted and observed outcomes in the 1-, 3-, and 5-year OS. Remarkably, IGBC has unique characteristics, such as a few patients with distant metastasis and iatrogenic peritoneal metastasis often derived from bile spillage that occurred at initial surgery. Therefore, M status was excluded from the nomogram, while peritoneal metastasis and the other 4 variables were included in the nomogram, and the nomogram was more accurate than the AJCC TNM staging system for predicting the prognosis of patients with IGBC.

However, some limitations need to be considered in this study. First, it was a retrospective single-center study without external data validation, which may result in some bias and low accuracy, and further large-scale multicenter cohort studies are needed to validate our results. Second, the lack of relevant information on postoperative adjuvant chemotherapy and serum tumor markers may reduce the accuracy of our predictions, and future studies need to consider these variables. Despite these limitations, the nomogram model constructed in this study has excellent AUC values and calibration curves, making it an excellent model to provide physicians with accurate survival prediction.

5 Conclusion

In conclusion, based on the variables identified in this study, we successfully established a nomogram of IGBC for the first time. Well-calibrated nomogram survival curves can help physicians to make appropriate clinical decisions for individual IGBC patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

This study was approved by the institutional Review Board of Shanghai Eastern Hepatobiliary Surgery Hospital Ethics Committee (No. EHBHKY2022-K-025) and complied with its ethical standards. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Acquisition of data, analysis and interpretation of data: Z-HX, XS, M-QL, JW, J-XZ, K-JC, WL, R-LG. Writing-original draft: Z-HX, XS, M-QL. Writing-review and editing: allauthors. Supervision: X-QJ, Q-BC. All authors contributed to thearticle and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Weiqian Chen,
Zhejiang University, China
Rafael Morales Soriano,
Hospital Universitario Son Espases, Spain

*CORRESPONDENCE
Zhong Zeng
zzong@163.com
Ruolin Wu
wuruolin0685@126.com

†These authors contributed equally to this work

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Is percutaneous drainage better than endoscopic drainage in the management of patients with malignant obstructive jaundice? A meta-analysis of RCTs

Cnogwen Bian[1,2†], Yuan Fang[1†], Jun Xia[3], Lan Shi[4], Hanfei Huang[1], Qiru Xiong[5], Ruolin Wu[6*] and Zhong Zeng[1*]

[1]Department of General Surgery, The First Affiliated Hospital of Kunming Medical University, Kunming, China, [2]Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong SAR, China, [3]Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [4]Department of the Fourth Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China, [5]Department of General Surgery, The Second, Affiliated Hospital of Anhui Medical University, Hefei, China, [6]Department of Hepatopancreatobiliary Surgery and Organ Transplantation Center, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China

To compare the safety and efficacy of endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangial drainage (PTCD) in the treatment of malignant obstructive jaundice, a systematic review and meta-analysis of published studies was undertaken to assess the differences between the two procedures in terms of efficacy and safety. From November 2000 to November 2022, the Embase, PubMed, MEDLINE, and Cochrane databases were searched for randomized controlled trials (RCTs) on the treatment of malignant obstructive jaundice with ERCP or PTCD. Two investigators independently assessed the quality of the included studies and extracted the data. Six RCTs, including 407 patients, were included. The results of the meta-analysis showed that the overall technical success rate in the ERCP group was significantly lower than that in the PTCD group (Z=3.19, P=0.001, OR=0.31 (95% CI: 0.15-0.64)), but with a higher overall procedure-related complication incidence rate (Z=2.57, P=0.01, OR=0.55 (95% CI: 0.34-0.87)). The incidence of procedure-related pancreatitis in the ERCP group was higher than that in the PTCD group (Z=2.80, P=0.005, OR=5.29 (95% CI: 1.65-16.97)), and the differences were statistically significant. No significant difference was observed between the two groups when the clinical efficacy, postoperative cholangitis, and bleeding rate were compared.Both treatments for malignant obstructive jaundice were efficacious and safe. However, the PTCD group had a greater technique success rate and a lower incidence of postoperative pancreatitis.The present meta-analysis has been registered in PROSPERO

KEYWORDS

ERCP, PTCD, Malignant obstructive jaundice, Procedure-related complication, Meta-analysis

1 Introduction

Obstructive jaundice is caused by biliary stricture and bile excretion obstruction and is most commonly caused by malignant tumor compression or direct metastasis. Malignant obstructive jaundice (MOJ) can lead to pathophysiological disorders of multiple organ systems throughout the body, including systemic electrolyte imbalance, immune system injury, coagulation disorders, digestive system insufficiency, and malnutrition. If the obstruction cannot be removed in time, it may cause biliary infection, liver and kidney failure, and even death (1, 2). Most patients are diagnosed in the middle or advanced stages of the illness, and the tumors are unresectable. The incidence of radical resection among them is approximately 20% (3, 4), and the remaining patients may only select palliative therapy options, such as biliary drainage (BD).

There are many different types of biliary drainage operations in clinical practice, among which two types of procedures are prevalent: 1. Endoscopic retrograde cholangiopancreatography (ERCP): The endoscope is inserted into the descending part of the duodenum through the duodenal papilla into the bile duct, with the biliary stent placed through the site of the obstruction. ERCP, an effective treatment for obstructive jaundice, drains bile into the body or intestinal tract, quickly drains bile to relieve biliary obstruction and compression, removes jaundice, and improves liver function. 2. Percutaneous transhepatic cholangial drainage (PTCD): This procedure involves inserting an internal or external drainage cannula into the dilated bile duct through the liver under the guidance of X-ray or ultrasound to quickly discharge bile and ameliorate jaundice. With the continuous progression of endoscopic and percutaneous drainage, these procedures have gradually become the most effective methods known to alleviate MOJ; they can effectively reduce bilirubin levels in the blood, improve liver function, improve nutritional status, prolong life expectancy, and thus improve the quality of life, especially for obstructive jaundice with unresectable tumors. Therefore, ERCP or PTCD has become the initial treatment for obstructive jaundice, but the optimal treatment remains controversial.

In this study, we aimed to compare the differences in the technique success rate, clinical efficiency, and incidence of postoperative complications between the two methods through evidence-based medical analysis to evaluate the advantages and disadvantages of the two methods in the treatment of MOJ and to explore the best BD method for patients with MOJ.

2 Methods

Based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (5) and Cochrane Collaboration (6), we conducted the study with approval from the Institutional Review Board.

2.1 Search strategy and identification of studies

From November 2000 to November 2022, randomized controlled trials on the treatment of malignant obstructive jaundice with ERCP or PTCD were searched in the EMBASE, PubMed, MEDLINE, and Cochrane databases using the same index terms "ERCP, PTCD, PTBD, MOJ; endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangial drainage, malignant obstructive jaundice". The included literature had to be randomized controlled trials. Retrospective controlled trials, unpublished literature, case reports, and reviews were also excluded. Two researchers reviewed all of the literature and abstracts according to the study's requirements, excluding unqualified literature and reading the full text of any literature that could potentially be included to determine whether it met the inclusion criteria. All disagreements were resolved by discussion.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

All included investigations were English studies comparing PTCD and ERCP for malignant biliary obstruction. Subjects: Malignant obstructive jaundice is typically clinically diagnosed *via* imaging data as biliary stricture or occlusion caused by a primary or metastatic malignant tumor, such as pancreatic cancer, hilar cholangiocarcinoma, ampullary carcinoma, and other tumors. The patients were informed and agreed to participate in the study and provided written informed consent. Intervention measures in the experimental group: ERCP was used to treat malignant obstructive jaundice. The control group was treated with PTCD.

2.2.2 Exclusion criteria

Studies were excluded if they were nonrandomized controlled studies, incomplete randomized controlled studies, retrospective analysis studies, conference abstracts, complete texts without original data, duplicate reporting studies, letters, or review styles.

2.3 Data extraction and assessment of the risk of bias

Data on the publication year, authors, number of subjects, methodological characteristics, and evaluation indices (technique success, clinical efficacy, and procedure-related complications) were extracted. The bias risk assessment tool provided by the Cochrane Library was used to assess the quality of randomized controlled trials by two researchers independently, including the method of random allocation and whether subjects and study implementers and measurement results were blinded. The tool also assesses whether the data are complete and selective reporting of research results and other possible sources of bias. A consensus was reached after discussion when a controversy arose. Otherwise, divergence was resolved by third parties.

2.4 Statistical methods

The extracted data were statistically analyzed using the software package Rev Man 5.3. To compare outcomes, the odds ratio (OR) and

mean difference (MD) were calculated as effect sizes for dichotomous and continuous variables, respectively, including their combined value and 95% confidence interval (95% CI). A $\chi 2$ test was conducted to examine the heterogeneity among the included studies using the inconsistency index (I2) statistic. Heterogeneity was identified as P>0.10, I2>50%, in which a random-effects model was used; otherwise, the fixed-effects model was used for homogeneity, and two-sided P<0.05 was considered statistically significant.

3 Results

3.1 Study selection and trial characteristics

The search strategy identified 1432 articles, of which 154 duplicate articles were excluded, 1256 irrelevant articles were excluded after reading the titles and abstracts, and 22 articles remained initially. Full texts were assessed for eligibility (conference abstracts and full texts without original data for retrieval, duplicate published studies, letters, non-RCTs, retrospective analyses, and reviews were excluded). Finally, seven articles (7–13) were included in this study. Because of the immature technology recorded in the first RCT paper (12), there would have been significant heterogeneity if it was included, and the analysis would not truly reflect the efficacy and safety of the two procedures; consequently, that RCT was ultimately excluded. Figure 1 shows the literature search strategy and screening process, and the quality of the included studies is plotted in Figure 2. The primary characteristics of the included studies are shown in Table 1.

3.2 Technique success

The overall technical success rate was reported in all six articles, and there was no heterogeneity among the outcomes; therefore, a statistical analysis was conducted using the fixed effect model. The results of the meta-analysis: Z=3.19, P=0.001, OR=0.31 (95% CI: 0.15-0.64). The difference was statistically significant, and the total success rate of surgery in the PTCD group was significantly higher than that in the ERCP group (Figure 3).

3.3 Clinical effectiveness

The total clinical efficacy was reported in six studies, and heterogeneity was observed among the results of each study. The random-effects model was applied, and the results of the meta-analysis were as follows: Z=1.76, P=0.08, OR=0.46 (95% CI: 0.20-1.09), indicating that the difference was not statistically significant, and there was no significant difference in total clinical efficacy between the ERCP and PTCD groups (Figure 4).

3.4 Procedure-related complications

The incidence of overall procedure-related complications was described in six studies, and there was no heterogeneity among the results of each study. Statistical analysis was conducted using the fixed-effect model, and the results of the meta-analysis were as follows: Z=2.57, P=0.01, OR=0.55 (95% CI: 0.34-0.87), indicating

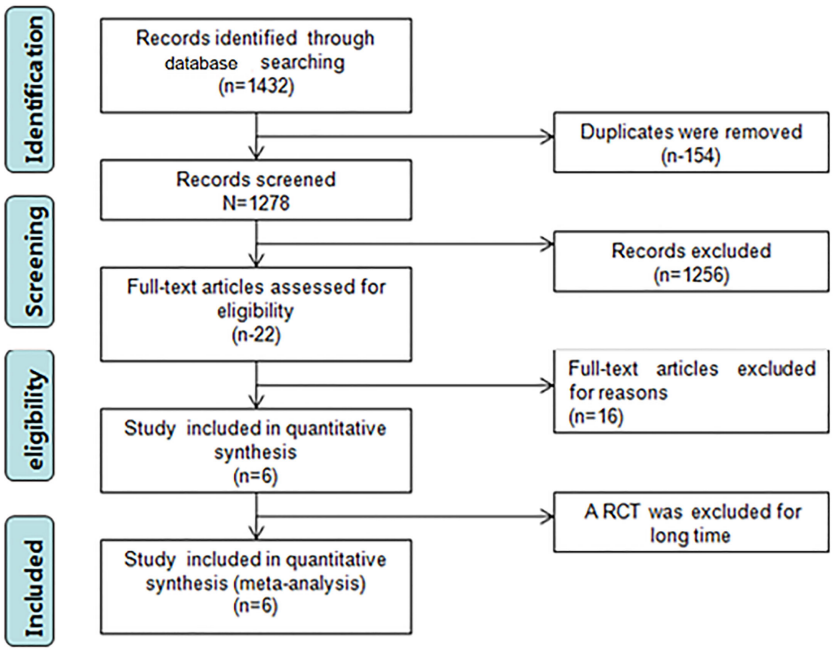

FIGURE 1
PRISMA flowchart summarizing the study selection process. The enrolled studies represent a total of 6 RCTs and encompass 207 patients with ERCP and 200 patients with PTCD. After quality assessment, all studies were interpreted as high-quality studies. The characteristics of the studies are depicted in Table 1.

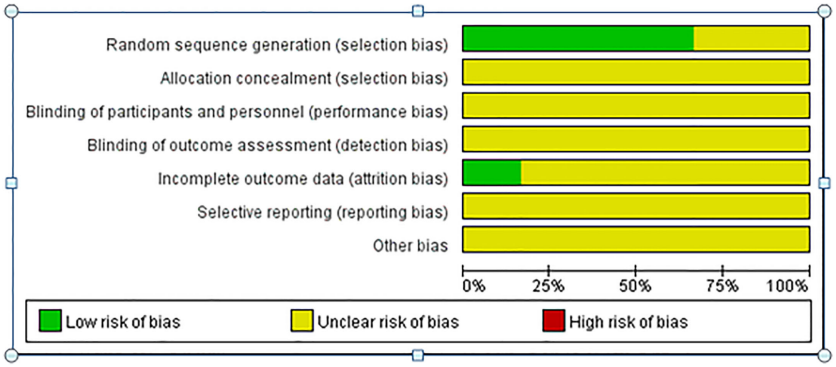

FIGURE 2
Quality assessment of the enrolled studies.

that there was a significant difference in the total complication rate between the two groups, with the PTCD group having a higher overall complication incidence (Figure 5).

3.5 Procedure-related cholangitis

The incidence of postoperative cholangitis was reported in all six articles, and there was heterogeneity among the results; thus, the random-effects model was used for statistical analysis. The results of the meta-analysis revealed Z=0.21, P=0.83, OR=0.87 (95% CI: 0.24-3.16), and there was no significant difference in the incidence of postoperative cholangitis between the ERCP and PTCD groups (Figure 6).

3.6 Procedure-related pancreatitis

Procedure-related pancreatitis was reported in all six articles, and there was no heterogeneity among the results; therefore, statistical analysis was conducted using the fixed-effect model. The results of the meta-analysis were as follows: Z=2.80, P=0.005, OR=5.29 (95% CI: 1.65-16.97). The difference was statistically significant, and the incidence of postoperative pancreatitis in the ERCP group was significantly higher than that in the PTCD group (Figure 7).

3.7 Procedure-related hemorrhage

There was no heterogeneity among the results; therefore, a fixed-effects model was used for statistical analysis. The results of meta-analysis: Z=1.90, P=0.26, OR=0.54 (95% CI: 0.19-1.58). The difference was statistically significant, and there was no significant difference in the postoperative bleeding rate between the ERCP and PTCD groups (Figure 8).

3.8 Publication bias

Publication bias analysis based on a funnel plot of technique success. No publication bias was detected with the observed indicators (Figure 9).

3.9 Sensitivity analysis

Sensitivity analysis is a crucial component of meta-analysis because it determines the overall credibility of the observed results. The results can be considered reliable if they remain consistent across sensitivity analyses. A meta-analysis of the remaining studies was conducted to assess the stability of the results. Individual investigations were eliminated item by item using a sensitivity

TABLE 1 Main characteristics of the included literature.

Author	Year	Country	Study Design	No. Patients in study		Technique success.		Clinical effective-ness		Complications	
				ERCP	PTCD	ERCP	PTCD	ERCP	PTCD	ERCP	PTCD
GH Bao, et al. (5)	2021	China	RCT	38	31	36	31	34	28	3	7
HM El-Haddad, et al. (6)	2021	Egypt	RCT	34	30	30	30	17	22	4	6
JS Coelen, et al. (7)	2018	Netherlands	RCT	27	27	20	25	17	21	18	17
SS Saluja, et al. (8)	2008	India	RCT	27	27	22	26	11	24	5	14
Virgı´nia P (11)	2002	Spain	RCT	26	28	15	21	11	20	9	17
XR Sun, et al. (9)	2014	China	RCT	55	57	52	55	49	55	11	3

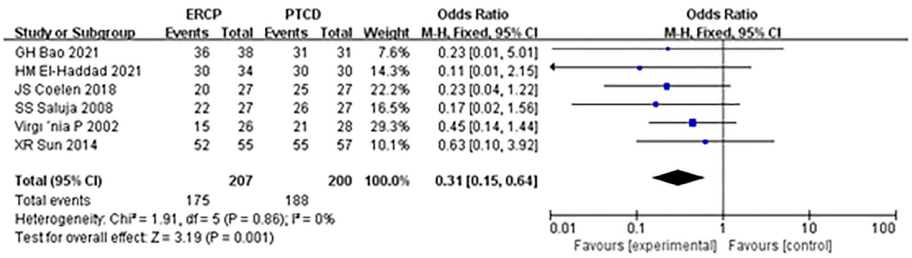

FIGURE 3
Forest plot comparing the technical success.

analysis. After excluding each study and reintegrating the effect values, all were within the CI. There was no significant difference before removal ($I^2 = 0$), showing that the sensitivity of the included literature was low and that the results of this analysis were stable.

4 Discussion

The methods of biliary drainage have been changing with the advancement of endoscopic technology, and PTCD became a prevalent technique in the late 1980s owing to its milder trauma, fewer comprehensive indications, and better economic benefits. PTCD helps restore physiological continuity to the biliary tract *in situ* and provides rapid relief of symptoms. Most patients with obstructive jaundice are treated with PTCD. Although the effect was significant and the prognosis could be improved, the incidence of postprocedural complications was still relatively higher (14, 15). With the improvement and availability of endoscopic technology, PTCD has been gradually replaced by endoscopic drainage (12, 16). However, such technical alternatives lack the support of EBM evidence from RCTs, that is, large-scale data on safety and efficacy from RCTs. Indeed, PTCD may increase the risk of local recurrence and metastasis (17).

In contrast, bile outflow may negatively affect digestive and liver functions. Therefore, some guidelines recommend ERCP as the preferred treatment for malignant obstructive jaundice (18). ERCP is more suitable for patients with physiological characteristics and can better restore the physiological drainage function of bile, improve quality of life, and relieve and delay liver failure.

4.1 Technique success and clinical effectiveness

This meta-analysis favors PTCD over ERCP for achieving satisfactory technical success as initial treatment in patients with MOJ. Otherwise, the two treatments had the same effectiveness in biliary drainage. A study (19) reported that the ERCP failure rate is approximately 10%, and the reasons for failure include immature techniques, ambiguous identification of the duodenal papilla, anatomical variation, and severe biliary tract stricture or occlusion caused by malignant obstruction. In comparison, PTCD has a higher procedure success rate than ERCP and can be recommended as the first treatment or remedy after ERCP treatment failure. Clinical effectiveness refers to the improvement in jaundice due to biliary drainage. A comprehensive comparison showed that both treatment methods can effectively decompress malignant biliary obstruction and drain bile. There was no statistically significant difference between the two groups in the clinical efficacy of the procedure for malignant obstructive jaundice (P=0.08). A larger-scale study (20) found that patients with morbidities of high obstruction, biliary sepsis, and liver function with a lower Child-Pugh classification would have poorer drainage effect, regardless of the difference in the patients' age, sex, diagnosis, number of stents, obstruction, bile duct diameter, abdominal cavity effusion time, intrahepatic lesion, lymph node metastasis, and distant metastasis. Except for these factors, the reason for the same clinical efficacy in the PTCD group following a higher technique success rate could be explained by the fact that ERCP has a better effect on bile drainage. Internal bile drainage is more favorable for bile acid excretion (21). Oral administration of the

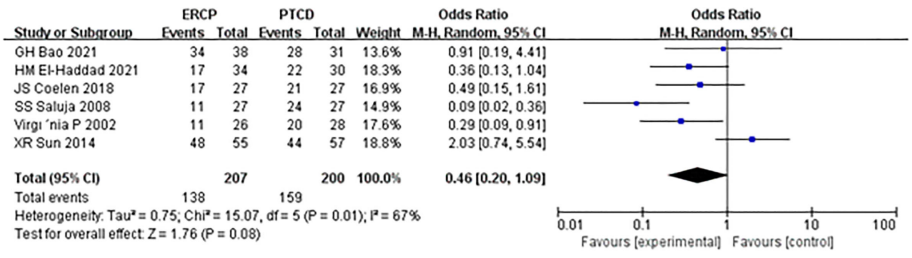

FIGURE 4
Forest plot comparing the clinical effectiveness.

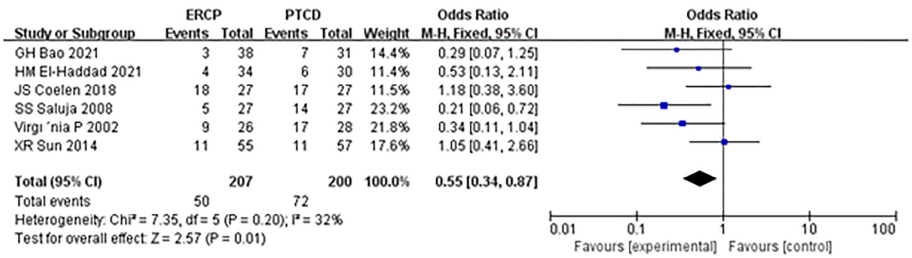

FIGURE 5
Forest plot comparing the overall complication rate.

lost bile from PTCD significantly shortened the time for total bilirubin to return to normal levels in the blood (22). In addition, the definition of clinical efficacy varied. For example, clinical effectiveness was defined as a 50% reduction in the serum total bilirubin level. In the study by Bao et al. (7), the time of decline was defined as less than two weeks, and in the study by Hany et al. (8), clinical effectiveness was defined as a 50% reduction in the serum total bilirubin level within ten days.

4.2 Advent effects

In this meta-analysis, ERCP was associated with fewer overall postprocedural adverse events and more procedure-related pancreatitis than PTCD, which is considered a prognostic factor in patients and a reference strategy in the management of MOJ. Mild complications affect the clinical efficacy in patients, while serious complications may cause disease progression or even lead to the death of patients. The mortality rates associated with ERCP and PTCD have been reported to be 0.1% and 2%, respectively (23, 24). In addition to the reasons for the operation itself, the experience of the operator and whether the operator has received systematic training are also correlated with the occurrence of postoperative complications (25). Short-term complications of ERCP and PTCD mainly include biliary infection, acute pancreatitis, hemorrhage biliary leakage, liver abscess, duodenal perforation, and pneumothorax, with an overall complication rate of 10% (26). In this study, there was a significant difference in the total incidence of postprocedural complications between the ERCP and PTCD groups (P=0.01), which differs from the results of another meta-analysis (27) published in 2017. There was an insignificant difference between the two groups, given that most of the included studies were retrospective. Postprocedural pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP). The incidence of ERCP-associated pancreatitis reported in the literature (28) is 2.1%-24.4%, and its high-risk factors include repeated intubation, incision of Oddi's sphincter, and accidental insertion of the main pancreatic duct (29). Subgroup analysis of the included studies showed that the incidence of postoperative pancreatitis in the ERCP group was significantly higher than that in the PTCD group, and the difference was statistically significant. Both the PTCD and ERCP groups were prone to cholangitis, and biliary obstruction was a high-risk factor for cholangitis. In addition, blockage of the drainage stent, stent displacement, and poor drainage effects are common reasons. However, there was no significant difference in the incidence of postoperative cholangitis between the two groups in this study (P=0.83). It was (30, 31) reported that operative bleeding after ERCP and PTCD was 1.6% and 2-3%, respectively. In this study, there was no significant difference in the bleeding rate between the two groups (P=0.26), which was inconsistent with another meta-analysis (32) and may be related to the small sample size and the need for a large RCT sample.

4.4 Strengths and limitations

This is the first meta-analysis to compare the efficacy and safety of ERCP with PTCD management of biliary obstruction based on definite RCTs. We systematically evaluated the short-term efficacy

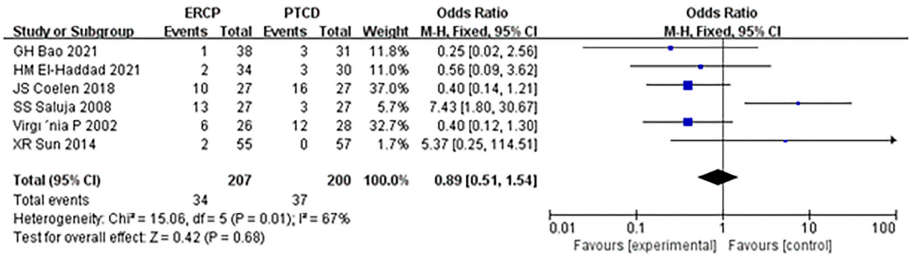

FIGURE 6
Forest plot comparing the incidence of procedure-related cholangitis.

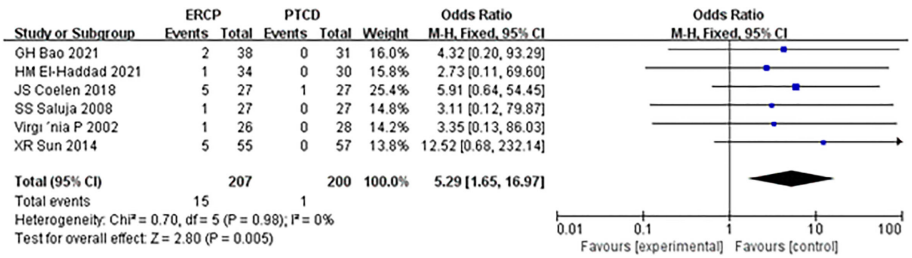

FIGURE 7
Forest plot comparing the incidence of procedure-related pancreatitis.

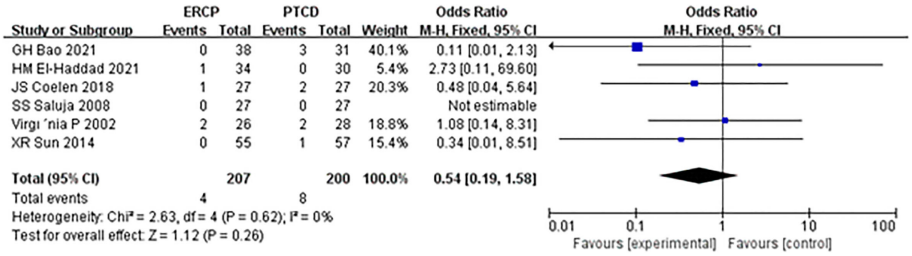

FIGURE 8
Forest plot comparing the incidence of procedure-related hemorrhage.

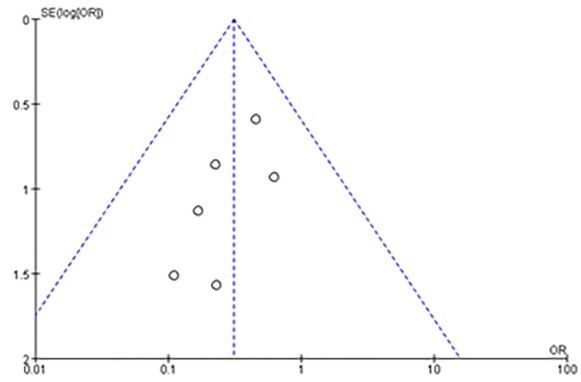

FIGURE 9
Funnel plot evaluating publication bias for technical success.

and safety of ERCP and PTCD for malignant obstructive jaundice in 6 RCT studies. However, there are still some shortcomings because the inherent limitations of the meta-analysis and the included studies may have weakened our analysis. We could not evaluate the long-term efficacy and safety because such data on 30-day mortality were only provided in one paper. In addition, due to such limitations, we could not analyze the efficacy and safety of different types of procedures. Additionally, there was heterogeneity in a few observation indicators in this study, attributed to the technical variance of operators in different institutions and long time spans, and our comparative analysis of specific complication rates and mortality was limited by the small sample size. Despite these limitations, we believe that our assessment is reliable for comparing the effectiveness and safety of the two methods.

5 Conclusion

Based on the available information and the acknowledged limitations of the datasets included in the present study, which incorporated data from 6 RCT studies that included more than 407 patients, the results of this meta-analysis suggest that PTCD is associated with more procedure-related and postoperative complications than ERCP. With regard to similar clinical efficacy, we recommend ERCP as the initial decompression of malignant biliary obstruction. In addition, both methods are technically demanding operations, and we recommend that unskilled surgeons perform them under supervision to ensure clinical safety.

Author contributions

CB and JX performed the search and drafted the manuscript. YF and HH performed the data extraction and analyzed the data. ZZ and

QX designed the study and amended the original draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Kittisak Jermsittiparsert,
University of City Island, Cyprus
Calin Cainap,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania
Yaying Sun,
Fudan University, China

*CORRESPONDENCE
Yi Tu
tuyi1027@sina.com
Zhengrong Li
lzr13@foxmail.com

†These authors have contributed equally to this work

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A bibliometric and visual analysis of publications on artificial intelligence in colorectal cancer (2002-2022)

Pan Huang[1,2,3†], Zongfeng Feng[1,2,3†], Xufeng Shu[1,2,3], Ahao Wu[1,2,3], Zhonghao Wang[1,2,3], Tengcheng Hu[1,2,3], Yi Cao[1,2,3], Yi Tu[4*] and Zhengrong Li[1,2,3*]

[1]Department of General Surgery, First Affiliated Hospital of Nanchang University, Nanchang, China, [2]Department of Digestive Surgery, Digestive Disease Hospital, The First Affiliated Hospital of Nanchang University, Nanchang, China, [3]Medical Innovation Center, The First Affiliated Hospital of Nanchang University, Nanchang, China, [4]Department of Pathology, The First Affiliated Hospital of Nanchang University, Nanchang, China

Background: Colorectal cancer (CRC) has the third-highest incidence and second-highest mortality rate of all cancers worldwide. Early diagnosis and screening of CRC have been the focus of research in this field. With the continuous development of artificial intelligence (AI) technology, AI has advantages in many aspects of CRC, such as adenoma screening, genetic testing, and prediction of tumor metastasis.

Objective: This study uses bibliometrics to analyze research in AI in CRC, summarize the field's history and current status of research, and predict future research directions.

Method: We searched the SCIE database for all literature on CRC and AI. The documents span the period 2002-2022. we used bibliometrics to analyze the data of these papers, such as authors, countries, institutions, and references. Co-authorship, co-citation, and co-occurrence analysis were the main methods of analysis. Citespace, VOSviewer, and SCImago Graphica were used to visualize the results.

Result: This study selected 1,531 articles on AI in CRC. China has published a maximum number of 580 such articles in this field. The U.S. had the most quality publications, boasting an average citation per article of 46.13. Mori Y and Ding K were the two authors with the highest number of articles. *Scientific Reports*, *Cancers*, and *Frontiers in Oncology* are this field's most widely published journals. Institutions from China occupy the top 9 positions among the most published institutions. We found that research on AI in this field mainly focuses on colonoscopy-assisted diagnosis, imaging histology, and pathology examination.

Conclusion: AI in CRC is currently in the development stage with good prospects. AI is currently widely used in colonoscopy, imageomics, and pathology. However, the scope of AI applications is still limited, and there is a lack of inter-institutional collaboration. The pervasiveness of AI technology is the main direction of future housing development in this field.

KEYWORDS

artificial intelligence, deep learning, colorectal cancer, bibliometrics, visualization, CiteSpace, VOSviewer

Introduction

Colorectal cancer (CRC) is currently the third most prevalent and the second most deadly cancer worldwide. As many countries' economies continue to grow, the incidence of CRC will increase (1, 2). In addition, the incidence of CRC is trending younger (3, 4).

Due to the increasing incidence of CRC, early screening and diagnosis of CRC are particularly important. Polyps cause most CRCs. This process begins with an aberrant crypt and progresses through 10-15 years, eventually leading to CRC (5). Colonoscopy with pathology biopsy is the standard for diagnosing CRC. However, there are still some limitations to endoscopic biopsy. The level of the endoscopist directly affects the detection rate of adenomas. Less experienced physicians can miss up to 50% of adenomas compared to skilled physicians (6).

Artificial Intelligence (AI) is a new technological science for research and development to simulate human intelligence. There are two main branches of AI in medicine: virtual and physical (7). Machine learning is a representation of the virtual part. It uses a large amount of existing data for algorithmic analysis to form a specialized logic set. This logic allows us to make judgments on new data (8). Imaging omics and predictive models belong to this category of applications. Another application of AI is mainly the application of physical devices. A typical example is various intelligent robotic systems, such as Da Vinci Robot-assisted Surgical Systems and intelligent care robots (9, 10). A study by Chen et al. (11) on applying deep neural network technology to colonoscopy showed that the system's accuracy was significantly better than that of general practitioners in screening for tumors and polyps. This study reveals the significant advantages of AI in information recognition. In the past five years, AI has been widely used to diagnose (12) and treat (13–15) CRC.

While the current use of AI in various aspects of CRC has yielded surprising results, we cannot ignore some of its disadvantages (16, 17). For example, AI can only train and build neural networks for a single task and cannot handle multiple tasks. AI also has significant limitations in treating rare diseases (18). In addition, considerable differences remain in the sensitivity, specificity, and accuracy of AI in CRC (19). Therefore, more randomized controlled studies are needed for further validation to improve the effectiveness and specificity of AI systems.

AI in CRC field is currently in the early stages of development. On average, more than 300 relevant studies are published each year, with the number continuing to grow. It has become a challenge for many scholars to keep abreast of the research and future trends. Bibliometrics is the discipline of quantitative analysis of literature using mathematical and statistical methods. Due to the rigor and objectivity of bibliometrics, scholars in many fields use this method to study the corresponding fields (20). We can use bibliometrics to analyze authors, journals, keywords, references, citations, and other information in specific databases to understand the current research structure and collaboration patterns in a field and to predict future research trends (21). Bibliometrics is now widely used in many fields (22–26). Our team has also researched the clinical applications of AI (27). However, as of now, there are no bibliometric studies related to AI in CRC.

Therefore, we hope to analyze the research process and status of research in the past 20 years and predict the possible future research trends by collecting the relevant literature on AI in the field of CRC from relevant databases. This study will help scholars in the area have a more systematic understanding of the research priorities and future research trends.

Method

Data source

Our data are from the Science Citation Index Expanded (SCI-EXPANDED) of the Web of Science Core Collection. Web of Science (WOS) is an extensive, comprehensive, multidisciplinary, core journal citation database containing more than 15,000 leading, high-impact journals and 50,000,000 publications in 251 categories and 150 research areas (28). Each article integrates the year, country and region, abstract, author, institution, document type, research field, journal title, citations, and references (29). Many scholars consider databases to be the most suitable for literature analysis.

Search strategy

We searched and collected literature related to AI in the field of CRC from January 1st, 2002, to September 30th, 2022. The type of literature was limited to Articles and Reviews, and the language was limited to English. We searched and screened all the papers within one day to ensure the consistency of the data. The data was exported to the WOS website as "full record and cited references" in "plain text format." Figure 1 shows the screening process.

The search formula is in the Supplemental File.

Data analysis and visualization

We conducted a bibliometric analysis of the documents retrieved. The main items analyzed were countries and regions, authors, institutions, citations and references, journals, and cited journals. Two investigators completed data analysis and checked independently to ensure study accuracy and reproducibility.

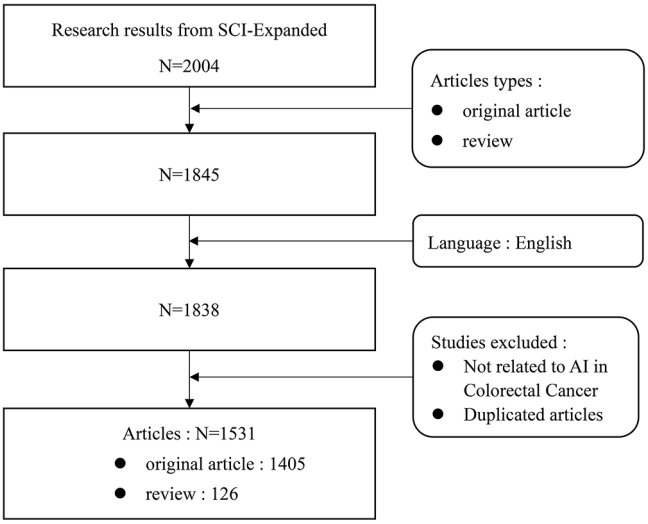


FIGURE 1
Flowchart of literature screening.

The H-index refers to a scholar with at most H papers cited at least H times each. Because it considers production and influence while resisting the bias of highly cited articles, it accurately reflects a scholar's scholarly achievements (30, 31). Impact factor (IF) is widely used to evaluate the impact of journals and is a simple yet effective indicator (32). We use the 2021 edition of Journal Citation Reports (JCR) and IF to assess the value of journals (33). The Altmetric Attention Score (AAS) is a new metric for assessing the impact of articles (34). It uses weighted algorithms to collect data from various origins, including news, Twitter, Google, Facebook, personal blogs, and other social media. It analyzes that data to demonstrate the impact of an article (35). The AAS can be accessed through a free search site (https://www.scienceopen.com/).

We used Microsoft Excel 2019 for flowcharts and statistical tables. We used the free statistics website (https://bibliometric.com/) and SCImago Graphica 1.0.25 for analysis and graphing of country and regional postings and collaborative postings. This study uses Citespace 6.1.R3 and VOSviewer 1.6.18 for the bibliometric analysis of countries, authors, journals, institutions, keywords, references, and citations. The primary analysis methods include co-authorship, co-citation, and co-occurrence, which are common in bibliometrics.

CiteSpace is a JAVA-based visualization software that allows visualization and analysis of academic literature in the research field. The analysis includes keywords, authors, journals, countries (36, 37).

VOSviewer is also a visualization software for bibliometric literature analysis, with similar functionality to Citespace (38). Compared to Citespace, VOSviewer's clustering analysis is more intuitive and aesthetically pleasing, and it can export data to SCImago Graphica for geographic visualization.

Ethics statement

The data used in this study were acquired from an open source and did not require approval by any ethical committee.

Result

Global publishing and collaboration trends

Following the literature search strategy flowchart, we collected 1531 papers from SCI-Expanded (SCI-E) over the past 21 years, including 1405 treatises and 126 reviews. These papers were published in 520 journals by 9126 authors from 2523 institutions in 77 countries. The articles cited 48,166 documents from 8794 journals.

Figure 2A shows that the number of articles issued each year gradually increases. Especially after 2019, the number of publications has multiplied. Among them, the papers published in 2020-2022 were over 300, 379 in 2021, and 354 in 2022 (9 months of data).

Bibliometric analysis of countries

The world map (Figure 2B) shows the volume of publications in each country in AI in CRC. As seen from the figure, research in this field is mainly concentrated in East Asia, North America, and Western Europe. The volume of papers is hugely unevenly distributed among countries.

The most published articles were by Chinese scholars (Table 1). They issued a total of 580 pieces, accounting for 37.9% of published articles, but the average citations for their papers were 16.06, which was at a medium level. It was followed by the US and the UK, with 361 and 136 articles, respectively. Only three countries have more than 100 articles, ten countries have more than 50, and the remaining countries have fewer articles. The most citations per article were in the United States, with 361 papers cited 16,653 times and 46.13 citations per article.

Figure 2C depicts the cooperation between countries. The US has the most comprehensive collaboration with other nations, including China, the UK, and Germany. The US, the UK, China, Germany, and the Netherlands collaborate the most in issuing articles. These head countries cooperate more closely, while other countries have weak cooperation.

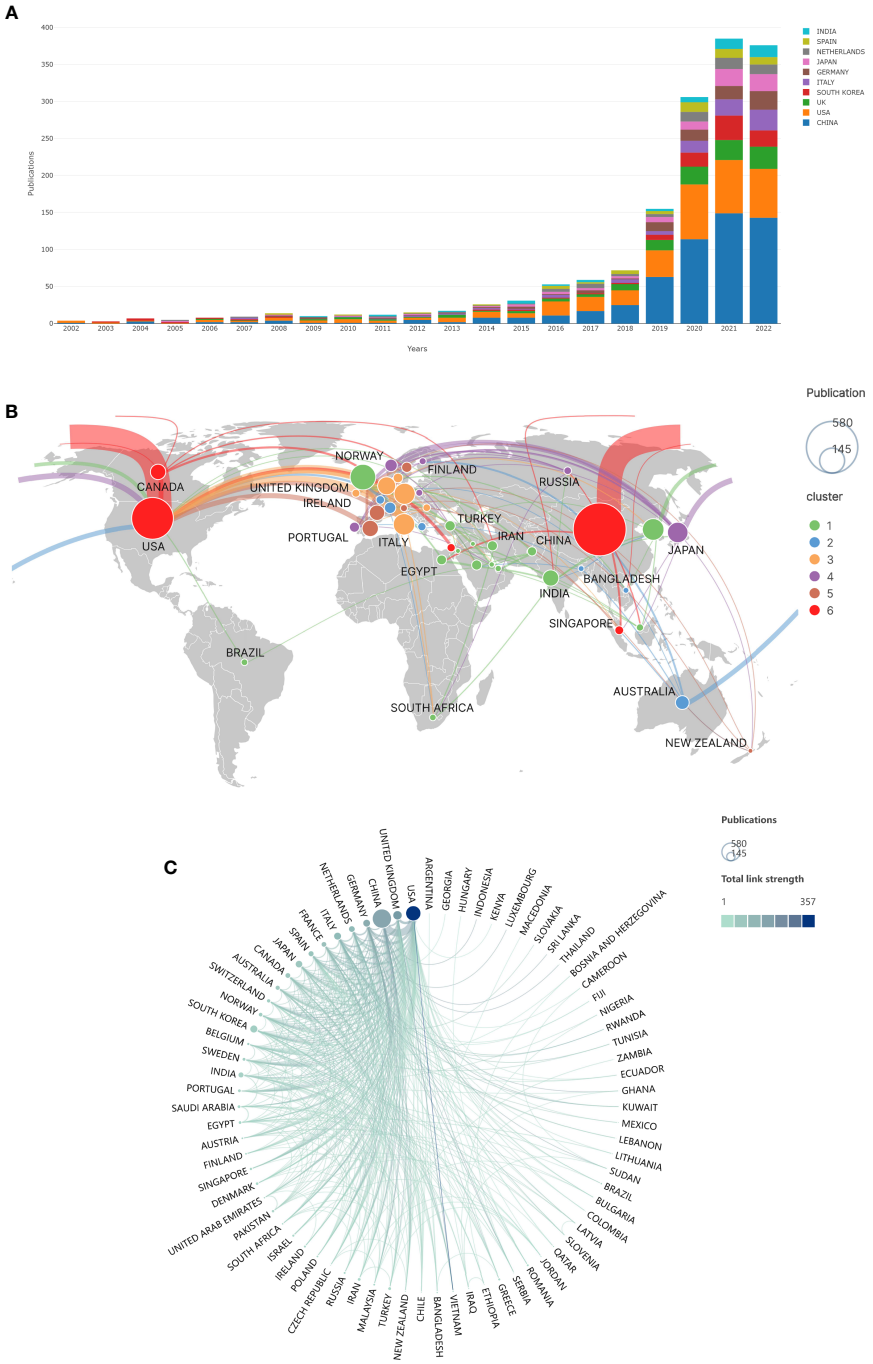


FIGURE 2
Publications and cooperation in different countries/regions of the world. **(A)** Top 10 countries/regions with annual publication trends of AI in CRC. **(B)** Map of the world's countries/regions in terms of publications and collaborations in the field of AI in CRC. (The size of the circle represents the number of articles issued. The thickness of the connecting line represents the number of collaborative communications between countries. The color of the circles represents the intensity of cooperation. Countries with the same color cooperate more frequently with each other.). **(C)** Cooperation between countries/regions (The size of the circle represents the number of articles issued, and the thickness of the line represents the intensity of cooperation between countries/regions.).

Bibliometric analysis of authors

We can understand the representative scholars and core strength of research in this field through the co-authorship analysis of the authors. We can calculate the minimum number of articles published by core authors in this field by Price's Law: $n = 0.749 \times \sqrt{n_{max}} = 2.48$ (n is the minimum number of papers published by core authors, and $n_{\max}$ is the maximum number of documents published by a single author in the field). Therefore, we import the data of authors with more than three articles into VOSviewer for visualization, and we can obtain the co-authorship visualization graph (Figure 3). As seen from the figure, there is a lack of collaboration between most authors. National scholars dominate collaboration among authors, and stable partnerships among international ones have not been formed.

We have listed the top 10 authors with the most published articles (Table 2). Among the 10 authors, Japanese scholars were the most

TABLE 1 Top 7 productive countries/regions related to AI in CRC.

Rank	Country	Publication	Citation	Publication/Citation
1	China	580	9317	16.06
2	USA	361	16653	46.13
3	UK	136	4006	29.46
4	South Korea	97	1089	11.23
5	Italy	95	1384	14.57
6	Germany	92	2345	25.49
7	Japan	87	1233	14.17

numerous (5), followed by Chinese scholars (4) and Dutch scholars (1). The most published articles were by Japanese scholar Yuichi Mori and Chinese scholar Kefeng Ding. In the field of AI in CRC, Yuichi Mori has published 11 articles with 290 citations and an average citation count of 26.36. He collaborated closely with Shin-Ei Kudo, Masashi Misawa, Kensaku Mori and other authors. The most numerous citation is by Chinese scholar Jie Tian, who has published ten papers in this field with a record of 1552 citations, with an average of 155.20 per paper. He also has the highest H-index, much higher than other scholars.

Analysis of journals and cited journals

A total of 520 journals published articles in this field, of which 74 journals published more than five articles. Twenty-eight journals published more than ten articles. We list the top 10 journals with the most publications in Table 3. The top 3 most published journals were *Scientific Reports* (51,3.33%), *Cancers* (46,3.00%), and *Frontiers in Oncology* (46,3.00%). Among the top 10 journals, the most cited journal was *Scientific Reports*, with 1,215 citations and an average citation rate of 23.82.

All papers cited references in a total of 8794 journals. We imported journal data with more than 200 citations into VOSviewer for visual analysis to obtain the co-citation web of cited journals (Figure 4A). The top three most-cited journals were *Gastroenterology* (1117 citations), *Scientific Reports* (1037 citations), and *Gastrointestinal Endoscopy* (951 citations). The cited journals consisted of four different color clusters. The green clusters are mainly for journals in Basic areas such as cell biology and molecular biology. The reason for citing these journals is to review the current research results and to provide theoretical support for their research. The blue and red clusters are clinically oriented journals in the field of gastrointestinal tumors. The yellow areas are journals in the field of computer science. Research often cites these journals to provide technical support.

We use Citespace to visualize the citing relations between citing and cited journals (Figure 4B). In the field of AI in CRC, there are 3 main

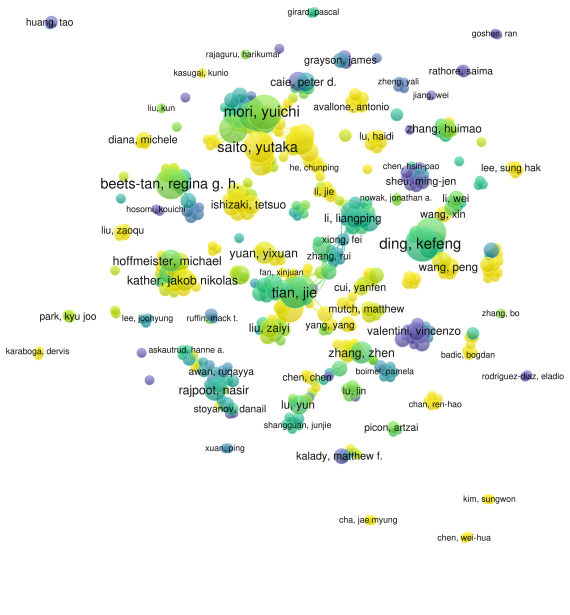


FIGURE 3
Visualization of co-authorship through VOSviewer (Circles represent the number of articles published. Connecting lines represent collaboration between authors. Colors represent the average year of authors' publications.).

TABLE 2 Top 10 authors by publications.

Rank	Author	Country	Count	Total citations	Average Citation	H-index
1	Yuichi Mori	Japan	11	290	26.36	29
2	Kefeng Ding	China	11	65	5.91	21
3	Jie Tian	China	10	1552	155.20	76
4	Regina G H Beets-Tan	Netherlands	10	247	24.70	12
5	Yutaka Saito	Japan	10	186	18.60	38
6	Jun Li	China	10	53	5.30	20
7	Masashi Misawa	Japan	9	283	31.44	26
8	Shin-Ei Kudo	Japan	9	239	26.56	19
9	Kensaku Mori	Japan	9	215	23.89	36
10	Zhenhui Li	China	9	80	8.89	6

areas of citing journals: (1) Medicine, Medical, Clinical; (2) Molecular, Biology, Immunology; (3) Mathematics, Systems, Mathematical. The cited journals are mainly in 6 fields: (1) Health, Nursing, Medicine; (2) Molecular, Biology, Genetics; (3) Systems, Computing, Computer; (4) Chemistry, Materia, Physics; (5) Psychology, Education, Social; (6) Environmental, Toxicology, Nutrition.

Analysis of research institutions

In AI in CRC, 2523 institutions have researched and published papers on the subject (Figure 5A). Of these, only 58 institutions published more than ten papers, and 186 institutions published more than five papers. We list the ten institutions with the highest publications and visualize institutional collaborations and citations.

The top three institutions with an enormous number of paper outputs were Sun Yat-sen University (51), Chinese Academy of Sciences (33), and Shanghai Jiao Tong University (33) (Table 4). The most cited institutions were, in order, Chinese Academy of Sciences (2047), Harvard Medical School (1212), and Southern Medical University (1212), which are also the three most cited institutions in terms of average citations (Figure 5B). Except for these large institutions, there is no gap in the number of articles published by most institutions. There is more cooperation between institutions within each country compared to the lack of cooperation between most inter-country institutions.

Co-occurrence analysis of keywords

We extracted keywords from these documents for analysis. The sum of keywords in 1531 papers was 5203, among which 107 keywords appeared more than 20 times. Keywords such as colorectal cancer (562), classification (233), machine learning (233), and deep learning (223) appear most frequently. We import the keywords with more than 20 frequencies into VOSviewer for visualization (Figure 6).

These keywords can be roughly divided into four categories (Figure 6A). The keywords in red are clustered around CRC and include secondary keywords such as expression, survival, feature selection, biomarker, and other secondary keywords. It is mainly about the training and recognition of CRC-related biometric features by AI technology, which belongs to basic research. The keywords of green clustering are mainly around Deep Learning, Computer-aided

TABLE 3 Top 10 most published journals in AI in CRC.

Rank	Journal	IF (2021)	JCR(2021)	Publication	Citation	Average Citation/Publication
1	Scientific Reports	4.996	Q2	51	1215	23.82
2	Cancers	6.575	Q1	46	265	5.76
3	Frontiers in Oncology	5.738	Q2	46	153	3.33
4	PloS One	3.752	Q2	26	331	12.73
5	IEEE Access	3.476	Q2	24	170	7.08
6	World Journal of Gastroenterology	5.374	Q2	21	209	9.95
7	Applied Sciences-basel	2.838	Q2	19	116	6.11
8	Computer Methods and Programs in Biomedicine	7.027	Q1	18	285	15.83
9	Computers in Biology and Medicine	6.698	Q1	17	302	17.76
10	Diagnostics	3.992	Q2	16	68	4.25

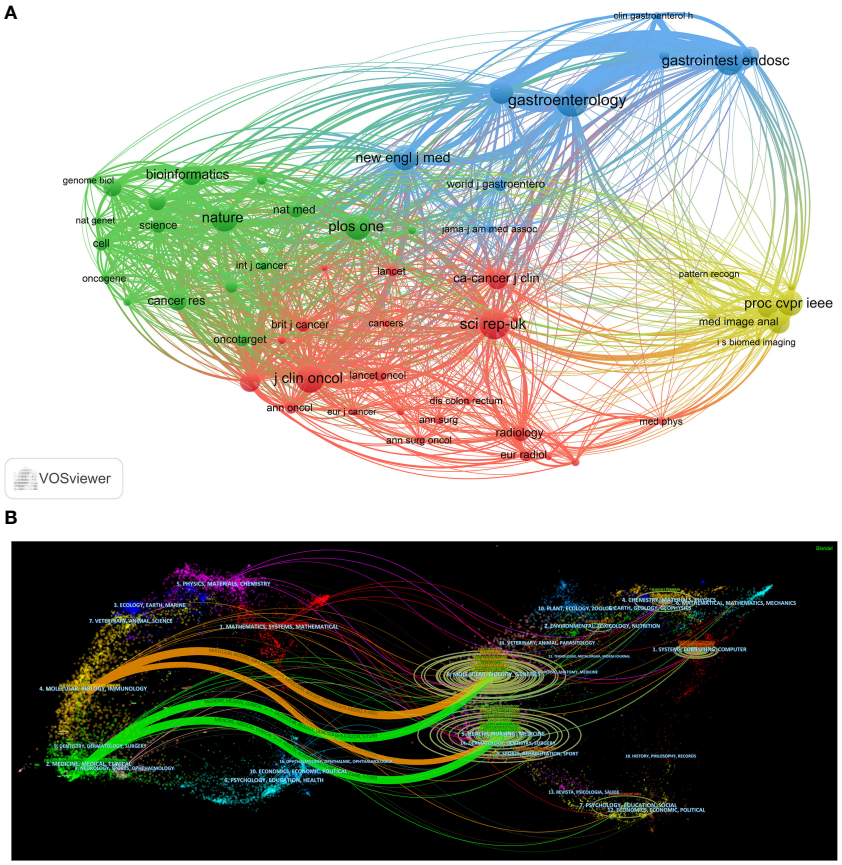


FIGURE 4
Citation relationship between journals. **(A)** Co-citation relationships between journals (The circles represent the number of articles cited by CRC in a journal, and the connecting lines represent a paper citing two different journals separately). **(B)** A dual-map overlap of journals on AI in CRC (On the left side are the citing journals. On the right side are the cited journals. The color represents the classification of journals. The curve is the citation line. The ellipse's long axis represents the number of papers cited in the same subject journal. The short axis of the ellipse represents the number of authors of papers in journals on the same topic.).

Diagnosis, Colonoscopy, and other keywords, which are mainly about classification, auxiliary diagnosis, and treatment of colonoscopic tumors. The blue and purple clusters have Machine Learning, Chemotherapy, and Radiomics as secondary keywords, mainly focusing on imaging and pathological examination of CRC. The yellow sets have fewer high-frequency keywords, such as Surgery and Resection, which are primarily related to the application of AI in the surgical treatment of CRC.

Figure 6B shows the average year of keyword appearances. As can be seen from the figure: Identification, Feature Selection, and other keywords appeared earlier, mainly before 2018, while Deep Learning, Artificial Intelligence, radiomics, and different keywords appeared more often after 2021. This picture also indicates that the hot research topics in the last few years have concentrated on deep learning, colonoscopy, polyp segmentation, and radiomics.

If some keywords are concentrated in a certain period, we can call them to burst words. Burst words can reflect different stages of development in a field. We extracted the top 20 most breaking keywords from AI papers in CRC by Citespace (Figure 6C). AI in CRC first emerged in 2002. After 2015, the duration of burst words gradually shortened. The keyword with the highest burst intensity is the support vector machine.

Analysis of articles and references

We screened 1531 publications from the field, 41 of which were quoted over 100 times. We presented the top 10 publications with total citations (Table 5). Guyon et al. (39) carried out a project on the application of support vector machines in gene selection, which received 5486 citations, much higher than other articles. Tajbakhsh et al. (40) and Huang et al. (41) followed, receiving 1379 and 928 citations, respectively. In the meantime, Wang et al. (42) and Urban et al. (43) have received many citations in AI in CRC. The AAS of Caravagna et al. (44) and Wang et al. (42) were much higher than the rest of the publications.

All articles cited 48166 references, 161 of which were quoted at least 20 times. We import them with more than 20 citations into VOSviewer for co-citation analysis and visualization (Figure 7A). The concerns are divided into four main clusters: articles in the green and yellow clusters are mainly related to computers and AI, and the references specifically provide technical support. The red and blue collections focus on specific applications of AI in CRC, where the red is mainly in imaging histology and pathology, and the blue is mainly in colonoscopy. Table 6 contains the top 10 references with the most citations. The most extensively cited article is Bray et al. (45), with 186

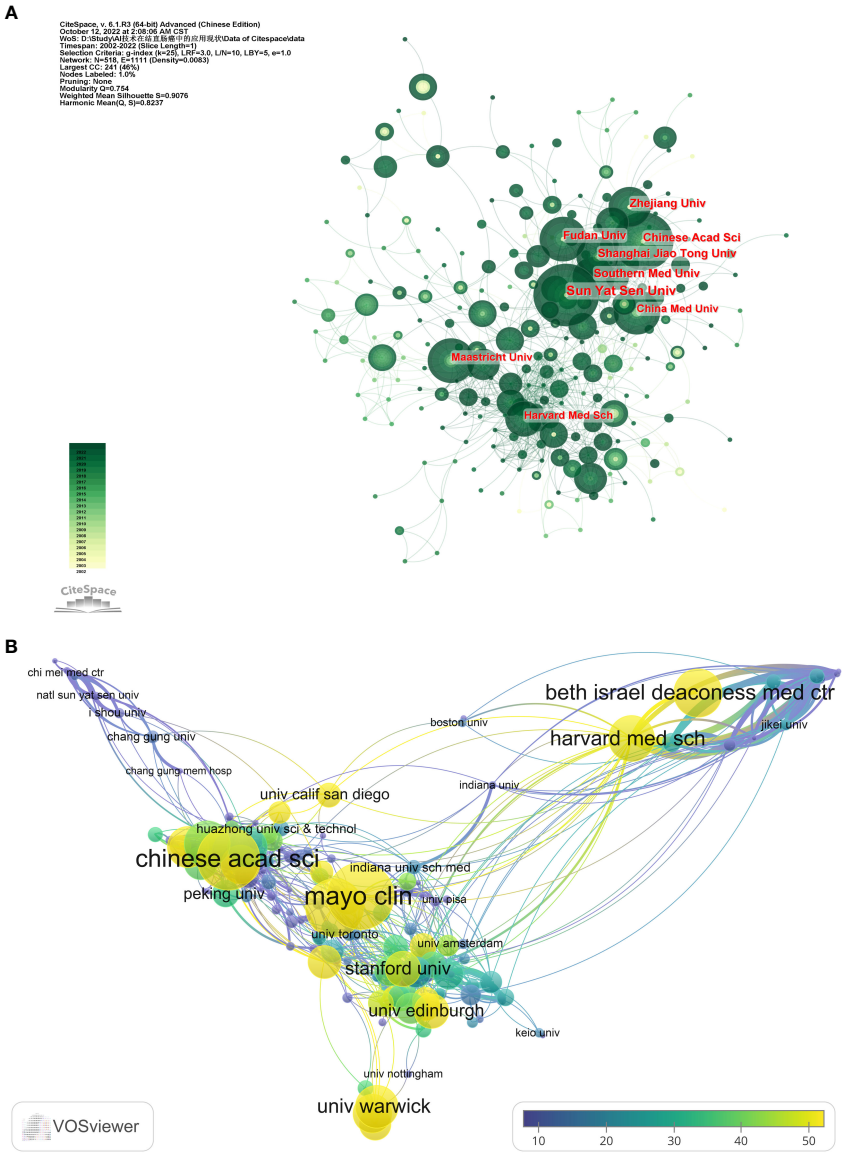


FIGURE 5
Cooperation and citations between institutions. (The circle size represents the number of articles issued by the institution. Connecting lines represent the intensity of collaboration between institutions.). **(A)** Cooperation among institutions. **(B)** Average citations per article by different institutions.

TABLE 4 Top 10 institutions with publications in AI in CRC.

Rank	Institution	Publication	Citation	Average Citation/Publication
1	Sun Yat Sen University	51	898	17.61
2	Chinese Academy of Sciences	33	2047	62.03
3	Shanghai Jiaotong University	33	311	9.42
4	Southern Medical University	30	1212	40.4
5	Zhejiang University	30	306	10.2
6	Fudan University	30	973	32.43
7	Maastricht University	26	649	24.96
8	Harvard Medical School	25	1212	48.48
9	China medical university	24	150	6.25
10	University of Oslo	21	626	29.81

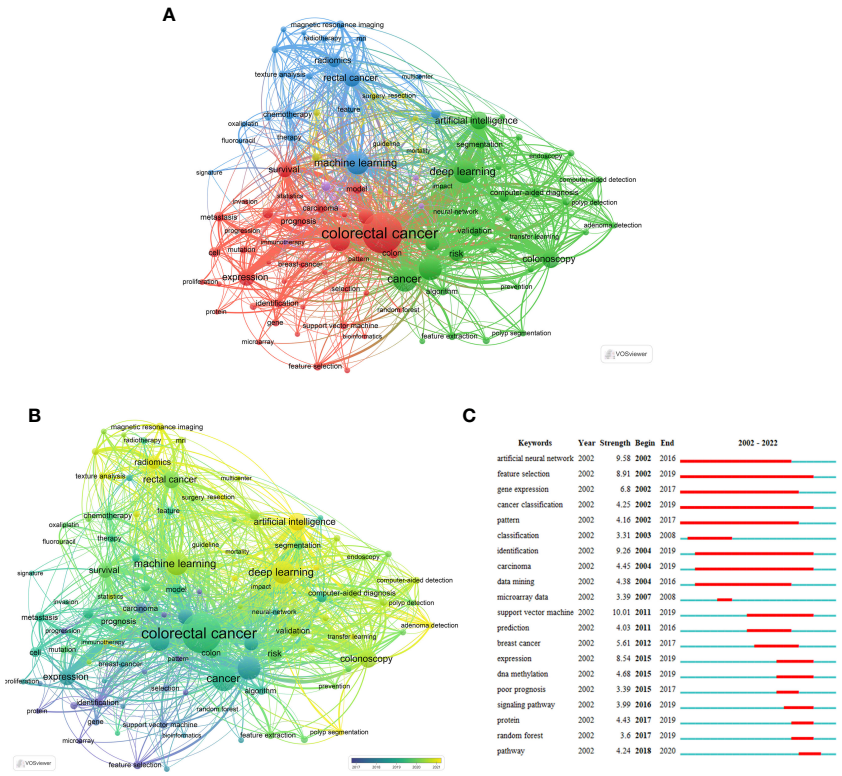
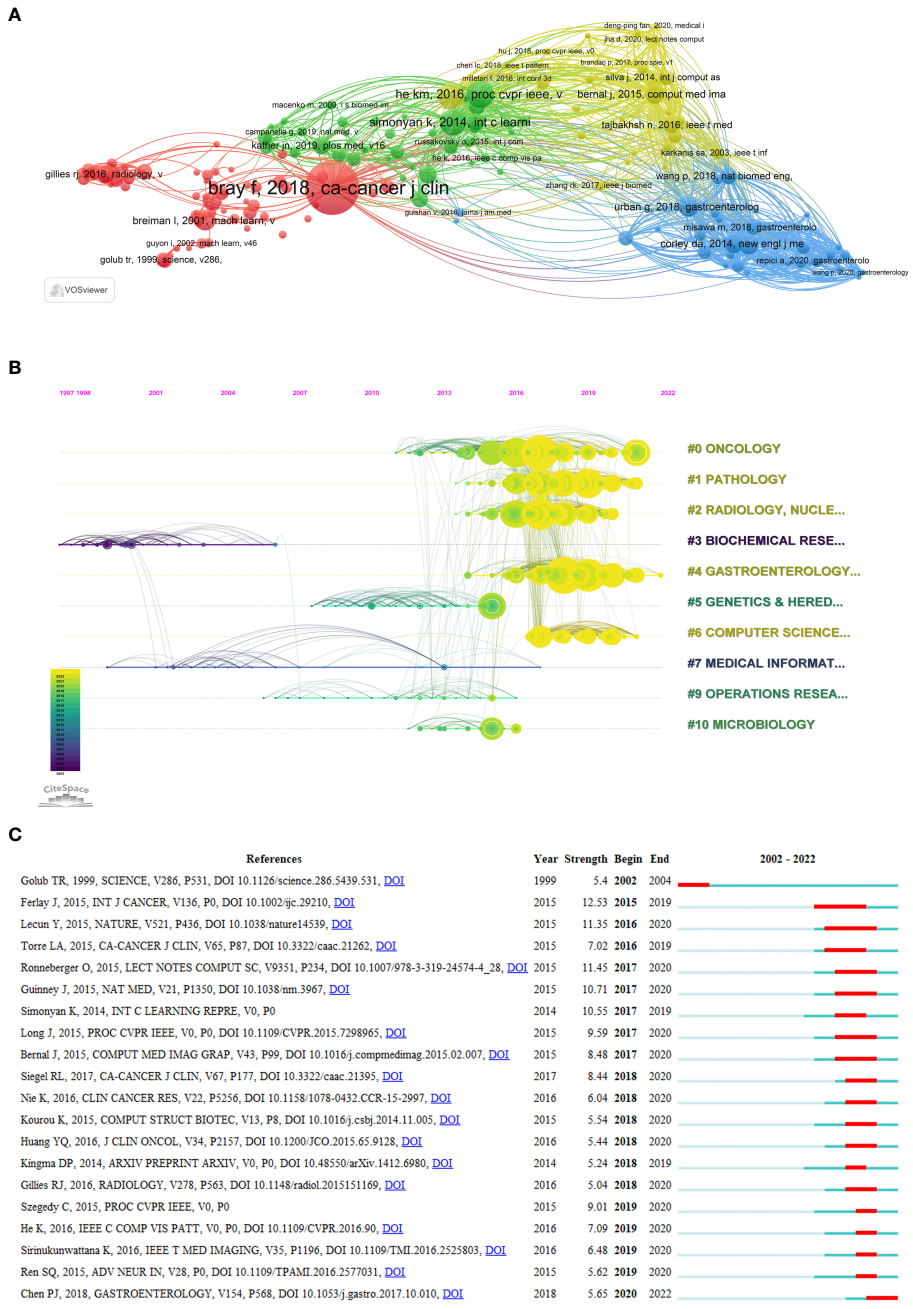


FIGURE 6
Co-occurrence analysis of keywords (The node size represents the frequency of keywords, the line between nodes represents two keywords appearing in the same document at the same time.). **(A)** Clustering view of keywords co-occurrence analysis (The node color represents keyword clustering.). **(B)** Temporal view of keywords co-occurrence analysis (The node color represents the average year of keyword occurrence.). **(C)** The top 20 burst words.

TABLE 5 Top 10 most cited articles.

Title	Journal	Author	Year	Citation	AAS
Gene selection for cancer classification using support vector machines	Machine learning	Guyon I; et al	2002	5486	27
Convolutional Neural Networks for Medical Image Analysis: Full Training or Fine Tuning?	IEEE Transactions on Medical Imaging	Tajbakhsh N; et al	2016	1379	41
Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer	Journal of Clinical Oncology	Huang, YQ; et al	2016	928	4
A Colorectal Cancer Classification System That Associates Cellular Phenotype And Responses to Therapy	Nature Medicine	Sadanandam A; et al	2013	660	76
Locality Sensitive Deep Learning for Detection and Classification of Nuclei in Routine Colon Cancer Histology Images	IEEE Transactions on Medical Imaging	Sirinukunwattana K; et al	2016	595	15
Detecting Repeated Cancer Evolution from Multi-Region Tumor Sequencing Data	Nature Methods	Caravagna G; et al	2018	474	629
Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy	Gastroenterology	Urban G; et al	2018	309	58
Real-Time Automatic Detection System Increases Colonoscopic Polyp and Adenoma Detection Rates: A Prospective Randomized Controlled Study	GUT	Wang P; et al	2019	294	594
Gene Expression Patterns Unveil A New Level of Molecular Heterogeneity in Colorectal Cancer	Journal of Pathology	Budinska E; et al	2013	274	24
The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges	Theranostics	Liu ZY; et al	2019	272	1



C

References	Year	Strength	Begin	End	2002 - 2022
Golub TR, 1999, SCIENCE, V286, P531, DOI 10.1126/science.286.5439.531, DOI	1999	5.4	2002	2004	
Ferlay J, 2015, INT J CANCER, V136, P0, DOI 10.1002/ijc.29210, DOI	2015	12.53	2015	2019	
Lecun Y, 2015, NATURE, V521, P436, DOI 10.1038/nature14539, DOI	2015	11.35	2016	2020	
Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	7.02	2016	2019	
Ronneberger O, 2015, LECT NOTES COMPUT SC, V9351, P234, DOI 10.1007/978-3-319-24574-4_28, DOI	2015	11.45	2017	2020	
Guinney J, 2015, NAT MED, V21, P1350, DOI 10.1038/nm.3967, DOI	2015	10.71	2017	2020	
Simonyan K, 2014, INT C LEARNING REPRE, V0, P0	2014	10.55	2017	2019	
Long J, 2015, PROC CVPR IEEE, V0, P0, DOI 10.1109/CVPR.2015.7298965, DOI	2015	9.59	2017	2020	
Bernal J, 2015, COMPUT MED IMAG GRAP, V43, P99, DOI 10.1016/j.compmedimag.2015.02.007, DOI	2015	8.48	2017	2020	
Siegel RL, 2017, CA-CANCER J CLIN, V67, P177, DOI 10.3322/caac.21395, DOI	2017	8.44	2018	2020	
Nie K, 2016, CLIN CANCER RES, V22, P5256, DOI 10.1158/1078-0432.CCR-15-2997, DOI	2016	6.04	2018	2020	
Kourou K, 2015, COMPUT STRUCT BIOTEC, V13, P8, DOI 10.1016/j.csbj.2014.11.005, DOI	2015	5.54	2018	2020	
Huang YQ, 2016, J CLIN ONCOL, V34, P2157, DOI 10.1200/JCO.2015.65.9128, DOI	2016	5.44	2018	2020	
Kingma DP, 2014, ARXIV PREPRINT ARXIV, V0, P0, DOI 10.48550/arXiv.1412.6980, DOI	2014	5.24	2018	2019	
Gillies RJ, 2016, RADIOLOGY, V278, P563, DOI 10.1148/radiol.2015151169, DOI	2016	5.04	2018	2020	
Szegedy C, 2015, PROC CVPR IEEE, V0, P0	2015	9.01	2019	2020	
He K, 2016, IEEE C COMP VIS PATT, V0, P0, DOI 10.1109/CVPR.2016.90, DOI	2016	7.09	2019	2020	
Sirinukunwattana K, 2016, IEEE T MED IMAGING, V35, P1196, DOI 10.1109/TMI.2016.2525803, DOI	2016	6.48	2019	2020	
Ren SQ, 2015, ADV NEUR IN, V28, P0, DOI 10.1109/TPAMI.2016.2577031, DOI	2015	5.62	2019	2020	
Chen PJ, 2018, GASTROENTEROLOGY, V154, P568, DOI 10.1053/j.gastro.2017.10.010, DOI	2018	5.65	2020	2022	

FIGURE 7
Analysis of reference citations (The circle represents the number of citations. The line represents two articles cited by the same article.). **(A)** Co-citation analysis of references (The colors represent the clustering of references.). **(B)** Timeline diagram of references (The color represents the average time the reference was cited.). **(C)** Top 20 references cited in burst.

citations, which focused on the epidemiological data of cancer. The following most cited articles were He et al. (46) and Ronneberger et al. (47), with 95 and 91 citations, respectively. In addition, these ten references, except Bray et al. (45), can be divided into two categories, one for theoretical studies of AI and one for studies of AI applications in clinical settings.

We can visualize the classification and publication time of the references by the timeline map (Figure 7B). Most of the literature was published after 2016 from the four categories of Oncology, Pathology, Radiology, and Gastroenterology. There were fewer co-citations of references between the different categories in the earlier period.

Figure 7C shows the references that were burst cited, and it is clear that there was a spike in burst cited references after 2016, indicating that the field of AI in CRC started to develop rapidly after 2016. The reference with the most burst strength is Ferlay et al. (48), who investigated the global epidemiology of cancer in 2012.

Discussion

AI technology has been evolving rapidly since its emergence and has been applied in several disciplines. The application of AI in CRC

TABLE 6 Top 10 references with the most citations.

Title	Journal	Author	Year	Citation	AAS
Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	CA: A Cancer Journal for Clinicians	Bray F; et al	2018	186	2454
Deep Residual Learning for Image Recognition	IEEE Conference on Computer Vision and Pattern Recognition	He KM; et al	2016	95	688
U-Net: Convolutional Networks for Biomedical Image Segmentation	Lecture Notes in Computer Science	Ronneberger O; et al	2015	91	263
Very Deep Convolutional Networks for Large-Scale Image Recognition	arXiv 2014	Simonyan K; et al	2014	90	313
Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy	Gastroenterology	Urban G; et al	2018	72	58
Random Forests	Machine Learning	Breiman L; et al	2001	71	155
Adenoma Detection Rate and Risk of Colorectal Cancer and Death	New England Journal Of Medicine	Corley DA	2014	70	701
WM-DOVA maps for accurate polyp highlighting in colonoscopy: Validation *vs.* saliency maps from physicians	Computerized Medical Imaging And Graphics	Bernal J; et al	2015	69	3
Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomized controlled study	GUT	Wang P; et al	2019	69	594
The consensus molecular subtypes of colorectal cancer	Nature Medicine	Guinney J; et al	2015	64	535

started in 2002 (39). Bibliometrics allows analysis of authors, institutions, countries, and references in SCIE literature databases to understand a research area and visualize it through Citespace and VOSviewer. This research approach is more comprehensive in analyzing the literature and presenting more intuitive results than a general systematic review. In AI in CRC, this research first uses bibliometrics to explore the applications and developments in the area from 2002 to 2022 and to speculate on future research trends.

AI in CRC research was slow to develop until 2015, with fewer than 30 publications per year, and a gradual rise began in 2016. After 2019, more than 100 papers are published each year and growing at a rate of more than 100 papers per year. The documents are expected to exceed 400 in 2022 (Figure 2A). This phenomenon indicates that the field is rapidly growing at the moment. The top three countries in this field published more than 1000 articles, accounting for more than 70% of publications from all nations. This result reveals a significant research gap between countries worldwide in this field, with the head country having a decisive advantage over the others. The overall amounts of articles contributed by Chinese scholars were 580. Still, the average number of citations per article is low, 16.06 per article, similar to other Asian countries such as Japan, Korea, and India. However, the average citations are still a gap between China and the Occident, suggesting that the quality of papers from China still has a particular hole compared with that from Europe & US. By digging deeper into the data, we found that China's annual publication volume begins to surpass that of the United States only after 2018 and will be twice as high by 2022. The average publication date for Chinese scholars is August 2019, compared to May 2018 for the US, which suggests that China is a late starter in this field but is developing rapidly, which may be one of the reasons for the low average citations. The US produced the second most published articles, with 361 in total, which received a staggering 16,653 citations, with an average citation rate of 46.13. It suggests that the US is at the core of this sector. Figures 2B, C show the collaborations among different nations. There is a substantial amount of cooperation between China and the US. Germany and the Netherlands, Italy, and other European countries cooperate closely. It shows that the cooperation between countries tends to be regionalized, such as Central Asia and West Asia cooperating more strongly, while European countries and cooperation are close too. However, the cooperation between regions is less, and language may be one of the reasons for this phenomenon.

Co-authorship analysis lets one learn about the collaborative relationships between authors in a discipline. Figure 3 shows that there is a lack of collaboration among most scholars. However, the extensive range of co-authorship networks among Japanese scholars suggests that cooperation between Japanese scholars is frequent. Table 2 contains the top 10 authors with the most papers, five of which are Japanese scholars. The most prolific author is Yuichi Mori, who has published 11 articles, and ten co-authored with four other scholars. The situation is similar for other Japanese scholars, which is the chieffactor in the large percentage of Japanese scholars in the table. Yuichi Mori's main research interests are the implementation of AI in colonoscopy, including increasing the diagnosis rate of colonoscopy through AI (49, 50) and predicting the effect of endoscopic tumor removal through AI (51, 52). Jie Tian is the most cited author among the ten authors, with a much higher average citation of 155.20. His H-index of 76 also proves that he is an influential scholar in this area of research. He focuses on the application of AI in histology and pathology imaging. Tian J et al. developed a radiomic columnar map for predicting lymph node metastasis in CRC preoperatively in 2016 (41). This paper has received 930 citations. Currently, he continues to delve into imaging histology, including training the AI to evaluate pathological response to neoadjuvant chemotherapy for rectal cancer *via* MRI (53–55). A survey of the impact of articles in this field (number of citations, AAS) gives us an idea of the critical academic results that have been achieved in this field (Table 5). Caravagna et al. (44) and Wang et al. (42) obtained 629 and 594

AAS, respectively, which were much higher than other scholars. The reason is that these two articles were retweeted several times on Twitter.

Articles in AI in CRC are published in a relatively scattered number of journals, with only 28 publishing more than ten articles. The top ten journals by publications are all excellent journals with JAR Q2 or above. Among them, *Scientific Reports* published 51 papers. They received 1215 citations, with an average of 23.82 citations, which is much higher than other journals, indicating that this journal has a significant influence in the field of AI in CRC. The top three journals were *Scientific Reports*, *Cancer*, and *Frontiers in Oncology*, with over 40 articles, much higher than the rest of the journals, indicating that these were more focused on research in this area. Scholars in this field can prioritize their results for publication in these journals. In addition, *Computer Methods and Programs in Biomedicine*, *Computers in Biology*, and *Medicine* have very high citations per article and are also excellent journals. These two journals mainly focus on computer principles (56–58), while Articles published in other journals focused on clinical applications. AI in CRC is an interdisciplinary field. The primary references in the published papers are from 6 areas, which indicates that the collaboration between fields is widespread and the field's future development will require closer collaboration between disciplines.

China accounts for 7 of the top 10 institutions, while the US, the Netherlands, and Norway each have one. China has a substantial amount of research institutions and publications, mainly due to the strong support of the Chinese government for AI applications in recent years, which has happened in almost all areas involving AI (59–63). It is foreseeable that, with increasing investment, China may be a leader in this field of research in the future. Each article published by the Chinese Academy of Sciences, Southern Medical University, and Harvard Medical School received more than 40 citations, indicating that they are the central institutions within the field.

The analysis of keywords provides another perspective on the development process and trends in this field. Figure 6A demonstrates that the keywords in AI in CRC can be divided into 4 clusters and combined with the period of the keywords in Figures 6B, C. We can divide the development of this field into two stages. The first stage is before 2018, mainly with red clustering keywords, such as Biomarker, Expression, Feature Selection, and Support Vector Machine. This is the technology reserve period, and scholars from various countries mainly conducted theoretical research on AI and the development of some basic applications. Guyon et al. (39) applied a Support Vector Machine to gene selection, and Chen et al. (64) and Lee et al. (65) improved the Support Vector Machine. On the other hand, Xu et al. (66) attempted to apply weakly supervised learning to classify pathological images. Keywords with blue and green clusters frequently appeared after 2018, such as Computer-aided Diagnosis, Machine Learning, Radiomics, and Colonoscopy, indicating that related research is starting to develop toward clinical applications. Urban et al. (43) applied CNN to colonoscopic adenoma screening, and Wang P et al. conducted several prospective studies on AI-assisted detection of adenomas (42, 67), all with satisfactory results. Several Meta-analyses (68, 69) have also confirmed the great advantage of AI technology in endoscopic adenoma detection. The application of AI in pathological examination has mainly focused on the identification of slides by AI assistance. Echle et al. (70) developed a deep learning-based system that directly detects CRC MSI by HE-stained slides. Yamashita et al. (71) also conducted a related study and showed that AI performed far better than experienced gastrointestinal pathologists. In addition, CT- or MRI-based imaging histology has many applications, including assessing pathological responses after radiotherapy or chemotherapy (72) and predicting colon cancer infiltration and metastasis (73, 74). The duration of keyword bursts was long before 2016 and became shorter after 2016 (Figure 6C). This phenomenon indicates that AI in CRC developed slowly before 2016 and entered a rapid development stage after 2016. The short burst duration due to the accelerated technology iteration may cause the inability to detect the outbreak of words in the line after 2020.

The analysis of co-cited references can reflect the reasons for the development of this field. Most of the highly cited references (46, 47) are from the field of computing (Table 6). It suggested that the development of AI technologies dominates the development of the field. There is still an explosion of citations, suggesting that this field is in a phase of rapid development.

In general, the application of AI in CRC can be divided into two phases. The first stage is 2002-2018, mainly involving the accumulation of AI technologies, and many scholars have conducted preliminary trials in this field. The second phase started from 2018 to the present. In this stage, AI technologies are beginning to apply to clinical applications, and the leading applications fall into three directions. The first category is the application in colonoscopy. Urban et al. (43) applied a convolutional neural network (CNN) to colonoscopy to improve the adenoma detection rate. The results showed that the accuracy of CNN in identifying polyps was 96.4%. Wang et al. (42) compared the real-time automatic polyp detection system with standard colonoscopy. They showed that the number of smaller adenomas detected by the AI system was much higher than that of the conventional examination (185 *vs.* 102). Repici et al. (75) reported similar results in their study. The second type of application is the application in imaging examinations. Lu et al. (76) applied R-CNN to MRI to predict lymph node metastasis and showed that the diagnosis time of AI was only 1/30 of that of imaging physicians. Cusumano et al. (77) developed a field-strength independent MR radiomics model to predict the achievement of pCR after neoadjuvant chemotherapy for rectal cancer and also achieved good results. The third type of application is in the pathology of CRC. Digital pathology (DP) can be used to obtain high-quality full-slide pathology image data by computer to form digital or virtual sections. AI powered by deep learning can process these medical images rapidly in a standardized manner and help pathologists improve their diagnostic efficiency and reduce their workload by outlining and rendering suspicious images in a structured language. Xu et al. (78) proposed a deep neural network-based method to classify, segment, and visualize large histopathological images. In the segmentation of malignant tissue glands, this method achieved 98% accuracy. Yamashita et al. (71) developed a deep learning model (MSINet) to predict microsatellite instability (MSI) in CRC. The results of external validation performed by the AI-trained model showed that the area under the receiver operating characteristic curve (AUROC) amounted to 0.865 (95% CI 0.735-0.995), while the average performance of the AUROC of the five pathologists was 0-605 (95% CI 0.453-0.757). The above study demonstrates the potential of AI deep learning applied to digital pathology to improve the quality and efficiency of pathology diagnosis significantly.

AI technology still has some shortcomings, and data is still the core part of AI. Deep learning of AI requires hugely high data quality, and data collection is challenging and expensive because of privacy and security issues. Secondly, AI technology currently builds models that only apply to a specific clinical range and become inapplicable once they go beyond that range. These limitations make it difficult for one AI model to be universally applicable worldwide. The security of AI system data is also an important issue that needs to be resolved. In addition, deep learning models often seem more like "black boxes," which are end-to-end learning designs that absorb data and generate output conclusions without explicitly explaining the rationale and process for their output conclusions (79). Therefore, the future development of AI in CRC may focus on the following two aspects. First, as globalization progresses, deep learning algorithms can train and learn using globally shared data and build an AI disease prediction model for patients worldwide. Second, the future AI can break the model bias directly through the most essential, fundamental features to build a model, quantify the features, explain the process of AI results, and solve the current "black box" problem.

Limitation

There are still some flaws in this study. First, the field's most recent and high-quality articles may be overlooked due to insufficient citations. Second, research is limited to English literature, and critical studies in other languages may be missed. What is more, research in the literature may have a certain lag in the current state-of-the-art research, which may bias the prediction of future directions.

Conclusion

Currently, AI has been widely used in the treatment of CRC. The main applications of AI today are in 3 areas. First, it is used in colonoscopy to improve the detection rate of adenomas and tumors at colonoscopy. The next is pathology, which can help pathologists identify pathological sections more quickly and accurately. The final is the application in imaging histology, mainly to predict the degree of infiltration and metastasis and to evaluate the efficacy of radiotherapy and chemotherapy. China and the United States are leading in this field, and the gap with other countries is still widening. Cooperation between most countries is still lacking. The future development of this field will largely depend on the availability of more significant accounts and more data sources for AI deep learning to improve its generalizability.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

PH and ZF conceived the study; ZW and TH collected the data; XS and AW checked and analyzed the data; PH and ZF wrote the paper; and YC, YT, and ZL reviewed and revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1077539/full#supplementary-material

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Kaiyuan Wang,
Tianjin Medical University Cancer Institute and Hospital, China
Juliette Hussey,
Trinity College Dublin, Ireland

*CORRESPONDENCE
Qian Wu
qian_wu2010@163.com

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Effect of short-term prehabilitation of older patients with colorectal cancer: A propensity score-matched analysis

Xiayun Wang[1,2], Ruizhe Chen[2], Lili Ge[2], Yifan Gu[1], Lin Zhang[1], Li Wang[1], Chengle Zhuang[1] and Qian Wu[1]*

[1]Department of Gastrointestinal Surgery, Shanghai Tenth People's Hospital Affiliated to Tongji University, Shanghai, China, [2]College of Medicine, Tongji University, Shanghai, China

Objective: The aim of this study was to assess the impact of short-term, hospital-based, supervised multimodal prehabilitation on elderly patients with colorectal cancer.

Methods: A single-center, retrospective study was conducted from October 2020 to December 2021, which included a total of 587 CRC patients who were scheduled to undergo radical resection. A propensity score-matching analysis was performed to reduce selection bias. All patients were treated within a standardized enhanced recovery pathway, and patients in the prehabilitation group received an additional supervised, short-term multimodal preoperative prehabilitation intervention. Short-term outcomes were compared between the two groups.

Results: Among the participants, 62 patients were excluded; 95 participants were included in the prehabilitation group and 430 in the non-prehabilitation group. After PSM analysis, 95 pairs of well-matched patients were included in the comparative study. Participants in the prehabilitation group had better preoperative functional capacity (402.78 m vs. 390.09 m, P<0.001), preoperative anxiety status (9% vs. 28%, P<0.001), time to first ambulation[25.0 (8.0) hours vs. 28.0(12.4) hours, P=0.008], time to first flatus [39.0(22.0) hours vs. 47.7(34.0) hours, P=0.006], duration of the postoperative length of hospital stay [8.0(3.0) days vs. 10.0(5.0) days, P=0.007), and quality of life in terms of psychological dimensions at 1 month postoperatively [53.0(8.0) vs. 49.0(5.0), P<0.001].

Conclusion: The short-term, hospital-based, supervised multimodal prehabilitation is feasible with a high degree of compliance in older CRC patients, which improves their short-term clinical outcomes.

KEYWORDS

multimodal prehabilitation, colorectal cancer, functional capacity, enhanced recovery after surgery, older adults

1 Introduction

Worldwide, with more than 1.9 million cases and 935.173 deaths a year, colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death (1) for which surgery is the main treatment. However, approximately one-third of patients who undergo colorectal resection experience postoperative complications (2, 3), which delay postoperative recovery, prolong hospital stays, lead to unplanned readmissions and reduce health-related quality of life (4). More than 65% of CRC patients are older than 65 years old (5). In the elderly, there is a progressive decline in the physiological function and reserve of several organ systems (6), which affects the tolerance to surgery. Older patients have a higher risk of postoperative complications, with a consequently longer postoperative hospitalization duration and a higher 30-day mortality rate (7–9).

Higher preoperative physical capacity levels are associated with a lower risk of postoperative complications and decreases in the postoperative hospitalization duration (10). However, medical staff target the postoperative period for rehabilitation and frequently neglect the assessment of and interventions for preoperative risk factors, such as malnutrition and frailty, and mental burdens such as anxiety and depression. Patients in the postoperative phase often experience pain, weakness, lack of sleep, etc. (11), and are thus more psychologically receptive to behavioral interventions in the preoperative period when scheduled to undergo major surgery (12, 13). "Prehabilitation" refers to interventions that enable patients to withstand an incoming stressor (10), which mainly includes the assessment of the patient's preoperative physical, nutritional, and psychological status and interventions. Kamarajah et al. (14) found that prehabilitation successfully reduces the risk of morbidity and postoperative complications. Recent studies (15, 16) have shown that multimodal prehabilitation programs, including interventions intended to enhance patients' functional capacity (17), nutritional status (18), and psychological status (19), were more effective than a single modality. However, the current prehabilitative interventions vary in terms of duration (4-12 weeks), site (home-based or hospital-based), modality (multi- or unimodal, with different components of exercise, nutrition, psychology, etc.), intensity, and outcome indicators. Systematic reviews (20–22) have identified the significance of high-intensity, long-term, individualized prehabilitation for improving the clinical outcomes of patients. However, adherence to long-term programs remains a significant barrier with regard to prehabilitation management. Considering the imperfection of the community-hospital medical structure in China, which is characterized by an imperfect management system and is ill-equipped for prehospital patient referral, prehospital education, and prehospital optimization (23), cannot ensure the smooth implementation of prehospital prehabilitation. Furthermore, due to the fear of cancer, most patients who are diagnosed with CRC are eager to undergo surgery as soon as possible. In China, most patients with gastrointestinal cancer routinely spend 3–12 inpatient days preparing for the operation (24, 25). Therefore, it is of interest to determine whether preoperative prehabilitation within this preparatory stay would be appropriate and feasible, based on the premise of not increasing the in-hospital stay.

Thus, the aim of our study is to investigate the feasibility and effectiveness of a short-term, hospital-based, supervised multimodal prehabilitation program for older CRC patients.

2 Materials and methods

2.1 Study design and participants

This single-center, retrospective study of older CRC patients was conducted at Shanghai Tenth People's Hospital from October 2020 to December 2021. In order to avoid intergroup contamination, patients were stratified into two groups prospectively at different periods based on whether they had implemented multimodal prehabilitation programs: the prehabilitation group included consecutively treated patients between July and December 2021, and the non-prehabilitation group of non-prehabilitation included consecutive patients who underwent surgery at the same hospital between October 2020 and June 2021, without multimodal prehabilitation programs.

Patients aged ≥65 years who were scheduled for elective CRC surgery were eligible for study participation. Patients were excluded if they (1) had a psychiatric history and could not understand instructions, (2) did not undergo surgery, (3) underwent emergency surgery, (4) had the new-adjuvant therapy before surgery; (5) were hospitalized for less than 5 days before the surgery, (6) had the American Society of Anesthesiologists (ASA) grade >III, (7) had premorbid conditions (i.e., cardiorespiratory, musculoskeletal) that contraindicated exercises, (8) received therapeutic diets or other conditions that precluded nutritional intervention, (9) had ≤50% adherence to the exercise prehabilitation program, or (10) refused to participate in this study. The study was registered at the Chinese Clinical Trial Registry (ChiCTR2000040928) and was approved by the hospital ethics committee (SHSY-IEC-4.1/20-205/01); all patients provided written informed consent for study participation.

2.2 Perioperative care

Both groups received the Enhanced Recovery After Surgery (ERAS) protocol in the perioperative period. Key aspects of this protocol include adequate preoperative health education, short preoperative fasting time (which included no fluid intake for 2 hours before surgery but received oral carbohydrates 2-3 hours prior to surgery), maintenance of normothermia, perioperative multimodal analgesia, removal of the catheter as early as possible, and early mobilization and feeding.

2.3 Prehabilitation management

In addition to standard ERAS-based care, patients in the Prehabilitation group (Prehab group) received individualized, supervised, in-hospital, and short-term multimodal prehabilitation. All patients received prehabilitation measures,

including exercise, nutrition, and psychological adjustment, for at least 5 days before surgery. The program duration was adapted to the surgical schedule and the prehabilitation program was formulated and began immediately after the baseline assessment of the patient by the multidisciplinary team on the day of admission. Prior to prehabilitation, all patients received the necessary education that was provided by a multidisciplinary team, which was mainly composed of the attending physician, kinesiologist, dietician, psychologist, and nursing staff. The attending physician mainly conducted the baseline assessment of the patient, whereas the kinesiologist, dietician, and psychologist made timely program adjustments for the implementation of prehabilitation, and the nursing staff provided adequate health education and undertook data collection from the patient. Instruction booklets with details of prehabilitation and a diary were delivered to patients to record the completion of prehabilitation every day.

2.4 Exercise intervention

To improve physical activity, patients were required to perform aerobic, resistance, and breathing training every day. (1) Aerobic exercise consisted of a 5-min warm-up, 20-min brisk walking or cycling, and 5-min cool-down. The resting heart rate and blood pressure were recorded before all supervised sessions. The target intensity of aerobic exercise was 60–75% of the heart-rate reserve. (2) Resistance exercise mainly consisted of 25 minutes of resistance exercises using different weight sandbags, and 5 minutes of stretching. Patients were provided with four sandbags (1, 3, or 5 kg, depending on the patient's ability) and trained in a sitting or standing position, with one sandbag in each hand, the hands held straight and parallel to the ground, and then lifted until the forearms were perpendicular to the upper arms. Two sandbags were tied to the patient's left and right ankles, and the patients were instructed to perform straight leg raising exercises in a sitting position, with both lower limbs straight and raised as high as possible, while alternating between the two lower limbs. (3) Breathing training mainly included 10 minutes of abdominal breathing training, which was intended to strengthen the diaphragmatic muscles and improve breathing efficiency. Patients were required to inhale slowly to the maximum lung capacity through the nose, hold their breath for a short time, and then slowly exhaled all the air through the mouth. All of the abovementioned exercises were performed 3 times/per day. The patient's first exercises were guided by a trained kinesiologist throughout the whole process, and the exercise plan was adjusted in time according to the patient's exercise situation. During the training, all patients were supervised by the same team of trained nurses, and the procedure was stopped if the patients had any obvious discomfort, such as shortness of breath, dyspnea, or exhaustion.

2.5 Nutritional intervention

The dietitian provided individualized diet plans for patients to improve caloric balance, bowel movement regularity, glycemic control, etc. Correct the patient's unhealthy eating habits by avoiding a high-calorie and, high-fat diet, eating more vegetables and fruits, and consuming more high-quality protein. A high-calorie diet was recommended for patients who did not meet their daily caloric needs. Patients with scores ≥3 on Nutritional Risk Screening 2002 (NRS 2002) (26) were identified as having a nutritional risk, and daily oral nutritional supplementation (ONS) was provided to achieve adequate protein intake (recommended intake 1.5 g/kg/d) (22). The protein supplement was ingested within 1 hour after exercise to facilitate muscle growth.

2.6 Psychological intervention

To alleviate negative emotions, the patients were taught how to channel their emotions and receive individualized guidance from a psychologist. Potential causes of perioperative fatigue, anxiety, and depression were discussed together by healthcare professionals. Nurses provided adequate health education to patients and corrected patients' misconceptions. The psychologist evaluates the patient's psychological condition, gives targeted counseling, and instructs the patient to listen to music before going to bed every day. Patients were instructed to perform 10 minutes of deep breathing exercises and meditation once a day.

2.7 Compliance and adherence to the program

Compliance with the multimodal prehabilitation program was deemed satisfactory when the patient preoperatively completed ≥75% of the scheduled exercise training tasks and fulfilled ≥75% of the protein supplementation intake and immunomodulatory formula. In our study, adherence to exercise training and psychological intervention was measured by calculating the percentage of actual exercise time versus program planned time, and adherence to the nutritional support was measured by the percentage of surplus and use of nutritional supplements compared to the required intake.

2.8 Data collection

All data were collected prospectively by two trained nurses. For each patient who was enrolled in this study, the following data were collected: demographic, perioperative, and outcome details.

Demographic data mainly included age, sex, education, occupation, marital status, body mass index (BMI), smoking, comorbidities, history of abdominal surgery, hypoalbuminemia (defined as serum albumin concentration <35 g/L), NRS-2002 score (26), and screening for frailty using the validated Modified Frailty Index (27) (score 0–1 indicates no frailty; and ≥2, indicates frailty).

Perioperative data included operative details, functional capacity, nutritional, and psychological outcomes. Operative details included tumor location, blood loss, type of surgery, surgical duration, and the ASA status. Functional parameters

included grip strength, gait speed, and the 6-min walk test (6MWT) (28, 29). Grip strength was measured by using an electronic hand dynamometer (EH101; CAMRY, Guangdong Province, China), and the maximal hand strength was recorded in three consecutive tests. Gait speed was calculated by walking 6 m from the starting point at the patient's usual speed, and an average of two measurements was taken. Furthermore, 6MWT (or 6-minute walk distance [6WMD]) was the distance that the patient walked back and forth in a 50-m corridor at the fastest walking speed in 6 minutes, and the 6MWD was the time it took for the patient to pass the 6-m distance at the fastest speed, and the results of two tests were averaged. Nutritional parameters included weight and triceps skinfold thickness. Triceps skinfold thickness was measured using a skinfold caliper, which pinches the skin and subcutaneous tissue of the patient's right arm at the deltoid muscle (at the midpoint of the line from the crest of the shoulder to the ulnar eminence) with the fingers, hold the skin fold by placing the two jaws of the measuring instrument under the fingers, and an average of two measurements was taken. Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (a score of 0–7 indicates a negative result and ≥8 indicates anxiety/depression) (30).

Outcome data included postoperative complications within 4 weeks after surgery according to the Clavien–Dindo classification (31), the total and postoperative length of hospital stay (LOS), hospitalization costs, time to bowel function recovery, time to first ambulation, 30-day mortality, and 30-day hospital readmissions. Postoperative follow-up assessment mainly included the patients' quality of life which was determined by using the 36-Item Short Form Survey (32) at 1, 3, and 6 months after surgery.

2.9 Statistical analysis

All data were collected prospectively and analyzed retrospectively. Descriptive analysis was performed on the baseline characteristics of the two groups. Categorical variables were presented as numbers (%), and numerical variables were expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR) according to the distribution. To minimize intergroup bias due to the nonrandom allocation of treatments between the two groups, analyses between the prehab and non-prehab groups were performed using propensity score-matching (PSM) and multiple logistic regression. The patients' propensity scores were calculated based on the following baseline factors: age, sex, education, occupation, marriage, BMI, smoking, NRS-2002, comorbidities, history of abdominal surgery, hypoalbuminemia, ASA, tumor location, type of surgery, blood loss, and duration of surgery. Participants in the prehab and non-prehab groups were then paired 1:1 in accordance with these propensity scores using a neighbor-matching algorithm without replacement, with a prespecified 0.02 standard deviation (33). Intergroup differences before and after the intervention in the two groups were compared using chi-square, Student's *t*-, and nonparametric tests. Linear or logistic regression was used to compare intergroup differences in the postoperative outcomes. All data were analyzed with the SPSS Statistics version 23.0 (IBM, Armonk, NY, USA). Two-tailed *P*-values <0.05 were considered statistically significant.

3 Results

A total of 587 CRC patients who were treated from October 2020 to December 2021 were assessed for eligibility in this study; 10 patients were excluded because they underwent emergency surgery or were unable to exercise, and the remaining 577 patients were included in this study. Subsequently, 59 patients were excluded during the study (reasons: died before surgery [n=1], underwent non-radical surgery [n=11], ≤50% adherence to the exercise prehabilitation [n=6], hospitalized for less than 5 days before surgery [n=16], and withdrew from the study midway [n=18]). Of the 18 patients who withdrew midway through the study, 5 withdrew because they perceived a lack of benefit, 2 found it difficult to adhere to the study procedures, and 11 withdrew because they refused to participate in the follow-up. Finally, 430 patients in the prehab group and 95 patients in the non-prehab group were included in the analysis. After a 1:1 ratio PSM, 95 patients were included in each of the two groups (Figure 1).

The participant characteristics are summarized in Table 1. Before matching, there were 95 patients in the prehab group and 430 patients in the non-prehab group. Patients in the prehab group were older ($P<0.001$), and had lower BMI ($P=0.009$) than participants in the non-prehab group. After the 1:1 ratio PSM, there was no significant intergroup difference ($P>0.05$) in terms of baseline and surgical characteristics.

In the prehab group, the median duration of the prehabilitation program was 7 days (interquartile range [IQR], 5–12). Adherence to exercise, nutritional, and psychological prehabilitation was 83.2%, 93.7%, and 100%, respectively. Compliance with the multimodal prehabilitation program was satisfactory in 79 (83.2%) patients.

After matching, data on intergroup differences before and after intervention are presented in Table 2. Compared to the non-prehab group, we found that multimodal prehabilitation improved 6MWD and reduced the anxiety scores of older patients ($P<0.05$). Data on postoperative outcomes are presented in Table 3. The prehab group had early ambulation [25.0 (8.0) hours *vs.* 28.0 (12.4) hours, $P=0.008$], shorter first flatus time [39.0 (22.0) hours *vs.* 47.7 (34.0) hours, $P=0.006$], and postoperative LOS [8.0 (3.0) days *vs.* 10.0 (5.0) days, $P=0.007$] than the non-prehab group. With regard to the quality of life (36-Item Short Form Survey), the prehab group had higher total mental SF-36 subscale scores 1 month after surgery than the non-prehab group [53.0 (8.0) *vs.* 49.0 (5.0), $P<0.001$]. No intergroup difference was found for the other clinical outcomes.

4 Discussion

In the current study, we focused on older CRC patients and adopted an in-hospital, supervised multimodal prehabilitation to improve patient compliance and ensure effective implementation of the prehabilitation program. To reduce bias due to the differences in age, BMI, and the duration of surgery between the two groups in

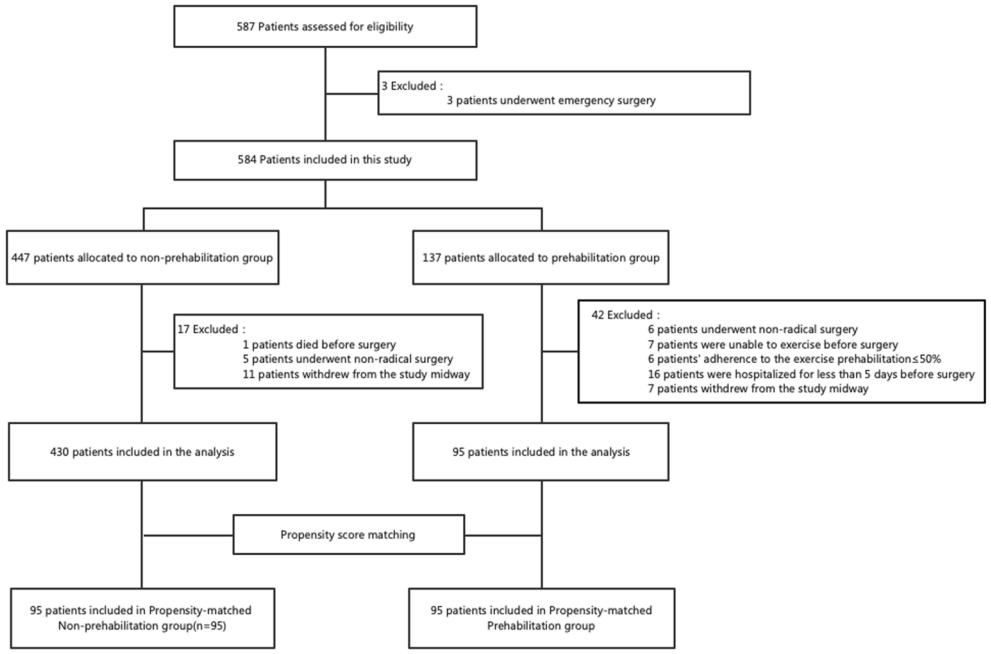

FIGURE 1
Flowchart of the patient selection process in the study.

this non-randomized controlled study, we adjusted the unbalanced baseline characteristics between the groups by using PSM analysis to ensure the reliability of the study.

The results from this study demonstrated that a short-term, hospital-based, supervised multimodal prehabilitation significantly improved short-term surgical outcomes in older CRC patients, including preoperative functional capacity, preoperative anxiety status, time to first ambulation, time to return to bowel function, duration of postoperative LOS, and quality of life in terms of psychological dimensions at the 1-month postoperative timepoint. We suggested that the additional prehabilitation might be a beneficial factor for early recovery after colorectal surgeries in the context of the standardized enhanced recovery protocol.

Patients in the prehab group received the prehabilitation program for different durations and not all patients had satisfactory compliance with the intervention. Several previous

TABLE 1 Baseline and surgical characteristics of the study cohort before and after matching.

	Unmatched comparison			Matched comparison		
	Prehab group (N=95)	Non-prehab group (N=430)	*P*-value	Prehab group (N=95)	Non-prehab group (N=95)	*P*-value
Age, median (IQR), years	71 (10)	67 (12)	<0.001*	71 (10)	70 (9)	0.401
Sex			0.569			0.762
Male	60 (63.2)	258 (60.0)		60 (63.2)	62 (65.3)	
Female	35 (36.8)	172 (40.0)		35 (36.8)	33 (34.7)	
Education			0.901			0.972
Primary school or less	24 (25.3)	96 (22.3)		24 (25.3)	23 (24.2)	
Junior high school	39 (41.1)	176 (40.9)		39 (41.1)	42 (44.2)	
High school	21 (22.1)	108 (25.1)		21 (22.1)	19 (20.0)	
College degree and higher	11 (11.6)	50 (11.6)		11 (11.6)	11 (11.6)	
Occupation			0.611			0.772
Retired	73 (76.8)	343 (79.8)		73 (76.8)	77 (81.1)	

(Continued)

TABLE 1 Continued

	Unmatched comparison			Matched comparison		
	Prehab group (N=95)	Non-prehab group (N=430)	*P*-value	Prehab group (N=95)	Non-prehab group (N=95)	*P*-value
Employed	7 (7.4)	31 (7.2)		7 (7.4)	6 (6.3)	
Unemployed	15 (15.8)	56 (13.0)		15 (15.8)	12 (12.6)	
Marriage			0.849			0.779
Married	89 (93.7)	409 (95.1)		89 (93.7)	91 (95.8)	
Unmarried	4 (4.2)	14 (3.3)		4 (4.2)	3 (3.2)	
Widowed	2 (2.1)	7 (1.6)		2 (2.1)	1 (1.0)	
BMI, mean ± SD, kg/m^2	23.65 ± 0.29	24.53 ± 0.14	0.009*	23.65 ± 0.29	23.47 ± 0.34	0.839
Smoking			0.605			0.620
Yes	10 (10.5)	38 (8.8)		10 (10.5)	8 (8.4)	
No	85 (89.5)	392 (91.2)		85 (89.5)	87 (91.6)	
NRS-2002			0.867			0.881
<3	36 (37.9)	159 (37.0)		36 (37.9)	37 (38.9)	
≥3	59 (62.1)	271 (63.0)		59 (62.1)	58 (61.1)	
Comorbidities						
Hypertension (Yes)	53 (55.8)	227 (52.8)	0.596	53 (55.8)	49 (51.6)	0.561
Diabetes (Yes)	20 (20.1)	76 (17.7)	0.441	20 (20.1)	16 (16.8)	0.459
History of stroke (Yes)	12 (12.6)	46 (14.9)	0.586	12 (12.6)	11 (11.6)	0.824
Previous abdominal surgery			0.173			0.583
Yes	17 (17.9)	105 (24.4)		17 (17.9)	20 (21.1)	
No	78 (82.1)	325 (75.6)		78 (82.1)	75 (78.9)	
MFI			0.169			0.510
0–1	68 (71.6)	336 (78.1)		68 (71.6)	72 (75.8)	
≥2	27 (28.4)	94 (21.9)		27 (28.4)	23 (24.2)	
Hypoalbuminemia			0.340			0.635
Yes	30 (31.6)	115 (26.7)		30 (31.6)	27 (28.4)	
No	65 (68.4)	315 (73.3)		65 (68.4)	68 (71.6)	
Tumor location			0.148			0.162
Colon	69 (72.6)	279 (64.9)		69 (72.6)	60 (63.2)	
Rectum	26 (27.4)	151 (35.1)		26 (27.4)	35 (36.8)	
ASA status			0.403			0.410
I	27 (28.4)	98 (22.8)		27 (28.4)	21 (22.1)	
II	62 (65.3)	293 (68.1)		62 (65.3)	64 (67.4)	
III	6 (6.3)	39 (9.1)		6 (6.3)	10 (10.5)	
Blood loss, ml			0.655			0.717
<150	77 (81.1)	340 (79.1)		77 (81.1)	75 (78.9)	
≥150	18 (18.9)	90 (20.9)		18 (18.9)	20 (21.1)	

(Continued)

TABLE 1 Continued

	Unmatched comparison			Matched comparison		
	Prehab group (N=95)	Non-prehab group (N=430)	*P*-value	Prehab group (N=95)	Non-prehab group (N=95)	*P*-value
Type of surgery			0.643			0.407
Laparoscopic	91 (95.8)	416 (96.7)		91 (95.8)	93 (97.9)	
Open	4 (4.2)	14 (3.3)		4 (4.2)	2 (2.1)	
Duration of surgery, hours			0.253			0.232
<3	76 (80.0)	320 (74.7)		76 (80.0)	69 (72.6)	
≥3	19 (20.0)	110 (25.6)		19 (20.0)	26 (27.4)	

BMI, body mass index; MFI, Modified Frailty Index; NRS-2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists.
Values in parentheses are percentages unless indicated otherwise.
*Statistically significant (P<0.05).

studies, including those by Barberan-Garcia et al. (34) and Carli et al. (35), have included supervised exercise in their interventions. Adequate prehabilitation compliance is necessary to ensure the effectiveness of prehabilitation. Some of the negative findings may be related to the relatively low adherence of patients to exercise programs (36). Similar findings were found in a study of prehabilitation in frail patients (35), where the adherence to exercise was only 68%, resulting in negative results in two groups. These findings suggest that although prehabilitation can potentially improve physiological reserve and functional capacity to promote early recovery, low adherence to prehabilitation can hinder the effectiveness of prehabilitation interventions. The compliance of 83.2% in the current prehabilitation program was comparable to the compliance in the previous multimodal tele-prehabilitation program (81%) (37) and was higher than that of the community-based prehabilitation program (56%) (38). Despite a short prehabilitation day, we demonstrated some improvement in the short-term clinical outcomes of older patients with CRC, suggesting that, for patients with short preoperative duration, preoperative implementation of short-term prehabilitation is a feasible and effective option to ensure patient compliance. Considering that the duration of the prehabilitation regimen should not cause a delay in surgery and that the length of the regimen should align with cancer waiting-time targets, we demonstrated the feasibility of implementing a short-term (5–12 days) preoperative intervention, which we believe this is more clinically relevant and easy to implement in China when compared to the 4–8week duration and ancillary support that is available before elective surgery.

Pecorelli et al. (29) have shown the value of the 6MWT as a gauge of increased functional capacity. Multiple studies (22, 39) have shown the effectiveness of prehabilitation in improving preoperative 6MWT in older patients. In this study, patients in the prehab group had improved preoperative 6MWT and better postoperative ambulation, which reduced the recovery time of postoperative bowel function and postoperative LOS. Potential explanations for these findings include the possibility that short-term prehabilitation enhanced patients' preoperative functional capacity, reduced surgical stress in patients, and faster recovery of postoperative gastrointestinal function, which led to a shorter postoperative hospital stay. Our study demonstrated that short-

TABLE 2 Pre- and post-intervention intergroup differences.

Variables	Prehab group (N=95)		Non-prehab group (N=95)		P_1	P_2	P_3
	Time 1	Time 2	Time 1	Time 2			
6MWD, mean ± SD, m	389.98 ± 76.76	402.78 ± 74.71	388.92 ± 84.42	390.09 ± 81.59	0.928	0.265	<0.001[c]
Grip strength, median (IQR), kg	24.90 (8.40)	25.00 (10.70)	24.90 (10.80)	25.40 (11.60)	0.284	0.264	0.202
Gait speed, median (IQR), m/s	1.03 (0.69)	1.12 (0.65)	1.19 (0.79)	1.10 (0.74)	0.132	0.254	0.762
weight, median (IQR), kg	60.15 (10.10)	63.00 (10.50)	60.70 (8.30)	61.00 (9.00)	0.721	0.818	0.104
Triceps skinfold thickness, median (IQR), mm	13.20 (4.30)	13.20 (4.60)	13.20 (4.60)	13.20 (4.30)	0.961	0.748	0.130
HADS-Anxiety[a]	24 (25.3)	9 (9.5)	18 (18.9)	28 (29.5)	0.294	<0.001[c]	NA
HADS-Depression[a]	8 (8.4)	11 (11.6)	13 (13.7)	16 (16.8)	0.247	0.299	NA

P_1 refers to the comparison between Time1 values in the prehab and non-prehab groups; P_2 refers to the comparison between Time2 values in the prehab and non-prehab groups; P_3 refers to the comparison between the difference in values between the prehab and non-prehab groups from before to after the intervention.
NA, not applicable.
[a]Values are expressed as number (%).
*Statistically significant (P<0.05).

TABLE 3 Intergroup differences in the postoperative short-term outcomes.

Outcomes	Prehab group (N=95)	Non-prehab group (N=95)	*P*-value
Postoperative complication[a]			0.764
None	65 (68.4)	66 (69.5)	
I	12 (12.6)	11 (11.6)	
II	12 (12.6)	15 (15.7)	
III	3 (3.2)	2 (2.1)	
IV	1 (1.1)	1 (1.1)	
V	2 (2.1)	0 (0.0)	
Total LOS, days[b]	16.0 (5.0)	15.0 (8.0)	0.098
Postoperative LOS, days[b]	8.0 (3.0)	10.0 (5.0)	0.007*
Time to first ambulation, hours[b]	25.0 (8.0)	28.0 (12.4)	0.008*
Time to first flatus, hours[b]	39.0 (22.0)	47.7 (34.0)	0.006*
Time to first defecation, hours[b]	89.0 (28.0)	89.0 (18.4)	0.104
Hospitalization costs, yuan[b]	70972.5 (15002.2)	66517.0 (14742.3)	0.149
30-day mortality[a]	2.0 (2.1)	0 (0.0)	0.155
30-day hospital readmission[a]	3.0 (3.2)	5.0 (5.3)	0.470
Total Physical SF-36 subscale[b]			
1-month after surgery	51.0 (5.0)	51.0 (5.0)	0.998
3-month after surgery	54.0 (9.0)	52.0 (10.0)	0.139
6-month after surgery	55.0 (16.0)	53.0 (9.0)	0.104
Total Mental SF-36 subscale[b]			
1-month after surgery	53.0 (8.0)	49.0 (5.0)	<0.001*
3-month after surgery	53.0 (10.0)	53.0 (9.0)	0.758
6-month after surgery	58.0 (17.0)	55.0 (15.0)	0.437

IQR, interquartile range; LOS, length of hospital days; OR, odds ratio; MD, mean difference; CI, confidence interval.
[a]Values are expressed as number (%).
[b]Values are expressed as median (IQR).
*Statistically significant (P<0.05).

term prehabilitation improved preoperative physical function but not nutrition before surgery, possibly suggesting that preoperative multimodal prehabilitation does not require all programs to be conducted simultaneously. This is very informative for designing future preoperative interventions to optimize engagement throughout the preoperative period according to the waiting days before surgery. For example, nutritional prehabilitation can be started as early as possible at the time of screening or diagnosis of CRC, whereas exercise prehabilitation and psychological prehabilitation can be started later, with emphasis on supervised training for patients in short-term prehabilitation, provided that the prehabilitation outcome is met.

Our study found that the total costs during hospitalization were not higher in the prehab group than in the non-prehab group, despite the increased preoperative nutritional costs for patients in the prehab group. These economic findings suggested that this prehabilitation protocol did not increase the economic burden on the participants. Potential explanations for these findings may include the sequentially better postoperative recovery in the prehab group, which led to a shorter postoperative LOS, reduced use of medication and medical care, and consequently, conferred lower in-hospital expenses. Consistent with the findings of Frederick et al. (40) and Carli et al. (35), we did not find a decrease in postoperative complications, mortality, etc. The lack of a prehabilitation effect in these variables may be explained by the fact that the patients in the non-prehabilitation group received ERAS care rather than conventional care, and the effect of short-term multimodal prehabilitation may be limited when other aspects of perioperative care have been optimized, or given the short duration of exercise, limited effects of the selected training regimen, or various other factors.

Psychological distress is common in cancer patients. Preoperative psychological interventions appeared to improve patient-reported outcome measures in several studies (41). In addition to the surgical outcomes, we found that prehabilitation reduced preoperative anxiety

and there was a progressive and significant improvement in QoL scores in the psychological dimension at the 1-month after surgery. This may indicate that patients' active participation in the process of psychological prehabilitation may contribute to diminish the emotional distress due to their major colorectal surgery. Furthermore, anxiety is a predictor of poorer recovery and potentially decreases adherence to exercise programs (42), which also reaffirms the important role of psychological prehabilitation in multimodal prehabilitation in our study.

This study had some limitations. First, our research was performed on patients from a single center and the sample size is relatively small, the number of postoperative deaths and readmissions was low, and further confirmatory studies are required to verify these findings. Second, the two groups of patients in this study were recruited at different times and with a small sample size of patients, there were differences between the two groups at baseline characteristics, but we have used PSM analysis to balance it between the two groups. Furthermore, we considered several obstacles to recommending prehabilitation for a high-risk population in terms of the need for pre-exercise evaluations and the risk for low adherence, and accordingly excluded some patients with a higher postoperative risk; therefore, our findings may not be generalizable to these high-risk populations.

In conclusion, the findings of our study demonstrated that meaningful changes in capacity function and clinical outcomes can be achieved with short-term, hospital-based, supervised multimodal prehabilitation in older patients who were scheduled to undergo radical resection of CRC. Furthermore, we suggested the importance of supervising patients during the prehabilitation process to improve the clinical outcome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of Shanghai Tenth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study design: QW and CZ. Acquisition of data: XW, LZ, YG, and LW. Analysis of data: XW, RC, and LG. Manuscript preparation: XW. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Suraj Venna,
Inova Health System, United States
Ludovico Carbone,
University of Siena, Italy

*CORRESPONDENCE
Yiqing Li
yiqingli_uh@126.com
Qin Li
li_qin@hust.edu.cn

†These authors have contributed equally to this work

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Case report: A case of delayed cutaneous metastases from signet-ring cell mixed-type gastric cancer

Shaohua Yao[1†], Peng Zhou[2†], Yiqing Li[2*] and Qin Li[2*]

[1]Department of Gastrointestinal Surgery, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen, China, [2]Department of Vascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Signet-ring cell gastric carcinoma is a highly malignant tumor, with the characteristics of strong invasiveness, rapid progression, a high degree of malignancy, and generally poor prognosis. The most common site of metastases is the abdominal organs, especially the liver, while delayed cutaneous metastases are rare.

Case presentation: We report a case of cutaneous metastases on the head, groin, and thigh, which recurred 7 years after signet-ring cell gastric carcinoma surgery. The patient was diagnosed with a 2.0×1.5×1.0cm tumor at the angle of stomach, and treated with Billroth II distal gastrectomy accompanied with D2 lymph node dissection. According the pathology, the stage was pT1N3M0. Then the patient received two cycles of oxaliplatin and tegafur chemotherapy, which was discontinued due to the inability to tolerate the side effects of chemotherapy. Seven years after the surgery, the patient initially presented with a fleshy mass on the head and beaded nodules in the groin; then, the mass gradually became larger, along with the thighs turning red, swollen, and crusty. Firstly, the patient was diagnosed with "lower extremity lymphangitis" and treated mostly with anti-inflammatory, promote lymphatic return, detumescence and elastic force cannula in vascular surgery department. However, the symptoms relieved insufficient. Finally, the skin biopsy indicates a signet-ring cell gastric carcinoma cutaneous metastasis. The whole-body PET-CT examination showed multiple nodules with increased metabolism. Then the patient was transferred to The Department of Oncology for further chemotherapy.

Conclusion: Our case highlights that gastric tumor recurrence and metastasis should be highly suspected when skin lesions appear in patients with signet-ring cell gastric carcinoma. At the same time, multidisciplinary consultation and close cooperation between surgeons, oncologists, and dermatologists are of great significance to the diagnosis and treatment of this disease.

KEYWORDS

signet-ring cell gastric carcinoma, cutaneous metastases, late recurrence, case report, post operative metastasis

Introduction

Cutaneous metastases of gastric carcinoma are extremely rare. Multiple studies have reported the prevalence of cutaneous metastases ranging from 0.2% to 2.2% (1), predominantly in males. The outcomes of postoperative gastric carcinoma are usually assessed by the 5-year survival rate. Cutaneous metastases generally occur within 1-3 years postoperatively, whereas reports of cutaneous metastases over 5 years are even rarer. Among histopathological subtypes of gastric carcinoma, signet-ring cell (SRC) carcinoma has a greater propensity for distant and cutaneous metastases. Furthermore, SRC gastric carcinoma is more prone to lymphatic metastasis compared with other histopathological subtypes of gastric carcinoma (2).

Case report

A 61-year-old man was admitted to our hospital in May 2022 for three progressively enlarging masses in the left groin area and head, along with redness and swelling of the left thigh for more than half a year. He had a history of a major gastrectomy in 2015 after being diagnosed with gastric carcinoma. The patient was diagnosed with a 2.0×1.5×1.0cm tumor at the angle of stomach, and treated with Billroth II distal gastrectomy accompanied with D2 lymph node dissection. The postoperative histopathology of the primary lesion was mixed invasive adenocarcinoma, of which signet-ring cell carcinoma accounted for 80%, and tubular adenocarcinoma accounted for 20% (Figure 1). The pathological stage was pT1N3M0. So, the patient received two cycles of oxaliplatin and tegafur chemotherapy, which was discontinued due to the inability to tolerate the side effects of chemotherapy. No tumor recurrence was found in the annual gastroscopy and CT-scan for 4 years after the operation; then, no follow-up was performed due to the COVID-19 epidemic.

However, after 6 years, the patient developed a beaded nodular tumor in the left groin area and two fleshy nodules on the scalp, accompanied by redness and swelling from the upper left thigh to the groin area; there was no obvious fever or pain. This patient was diagnosed with "lymphangitis of lower limbs" in several major hospitals and was prescribed anti-inflammatory and detumescence treatment. After repeated treatment, the tumor in the left groin area and scalp gradually increased, and the skin of the left lower

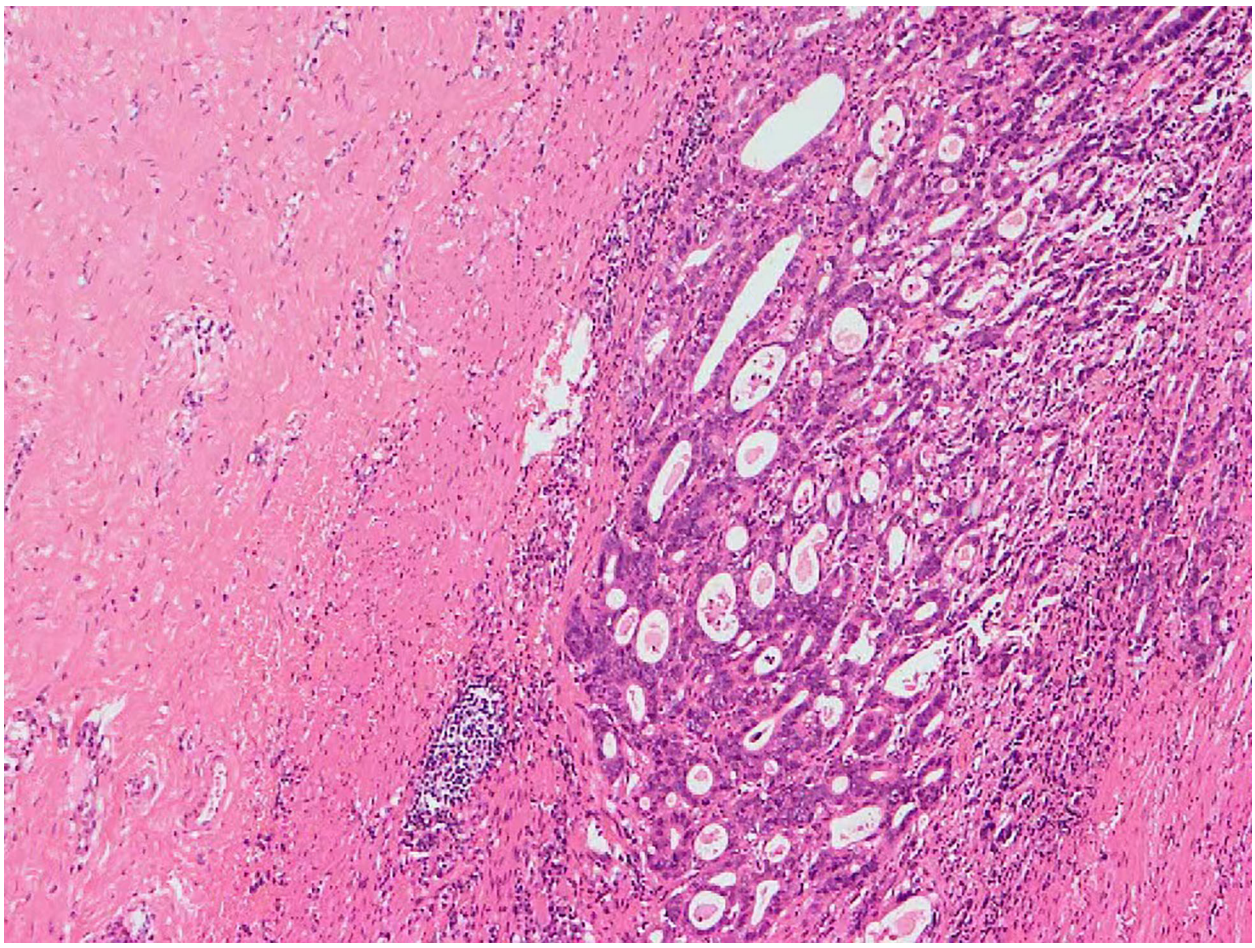

FIGURE 1
Postoperative pathology of gastric carcinoma in 2015.

extremity was red, swollen, and scleroderma-like. Finally, he came to our hospital for treatment.

A physical examination revealed moderate pitting edema of the left lower extremity, redness and swelling of the thigh with scleroderma-like changes, bead-like nodules of about 5*20cm in the groin area (Figure 2A), and two fleshy masses of about 3*3cm in size on the scalp (Figures 2B, C). The laboratory examinations showed that the blood routine, procalcitonin, liver, and kidney function were not abnormal, and the tumor markers carbohydrate antigen 72-4 and CA125 were elevated. A skin biopsy was performed on the groin mass, and the pathology showed metastatic poorly differentiated carcinoma, some of which were signet-ring cell carcinoma; immunohistochemical staining showed: PCK(+), CK7(+), CK20(-), CDX2(+), SATB2(-), and HER2(0) (Figure 3). A whole-body PET-CT examination showed multiple humus-like hypodense nodules on the skin surface from the left groin to the thigh, secondary lymphedema, and slightly increased metabolic diffusion (Figure 4A). There was also localized thickening of the skin on the top of the left head and back of the neck, and slightly increased metabolism. The above suggested the possibility of malignant tumor metastatic lesions (Figure 4B). After the diagnosis was confirmed, the patient was transferred to the oncology department for chemotherapy of Nivolumab combined with SOX. Four times of chemotherapy had been performed, and the efficacy was evaluated as reduced SD. Due to the COVID-2019 epidemic, the patient did not come to our hospital for subsequent chemotherapy treatment as planned.

Discussion

Cutaneous metastases usually develop from breast cancer, lung cancer, colorectal cancer, ovarian cancer, and other tumors (3), while metastases from stomach cancer to skin are extremely rare. Cutaneous metastases of gastric carcinoma are classified into the following three categories: (a) nodular, (b) inflammatory, and (c) sclerodermoid; the most common type is nodular type, followed by inflammatory (4). However, these three types occurred simultaneously in this case. The most common sites of metastases include the neck, back, abdomen, and inguinal regions. Meanwhile, the lesions can evolve into single or multiple nodules with an erysipelas-like morphology (also confirmed in this patient). Erysipelas carcinoma resembles an acute skin infection; different from skin infections, erysipelas carcinoma does not cause fever or leukocytosis, and antibiotics are ineffective (5). This case presented with a nodular appearance at first, followed by erysipelas-like changes and skin scleroderma-like changes in the lower extremities. After being treated as lymphangitis and lymphedema of the lower limbs in

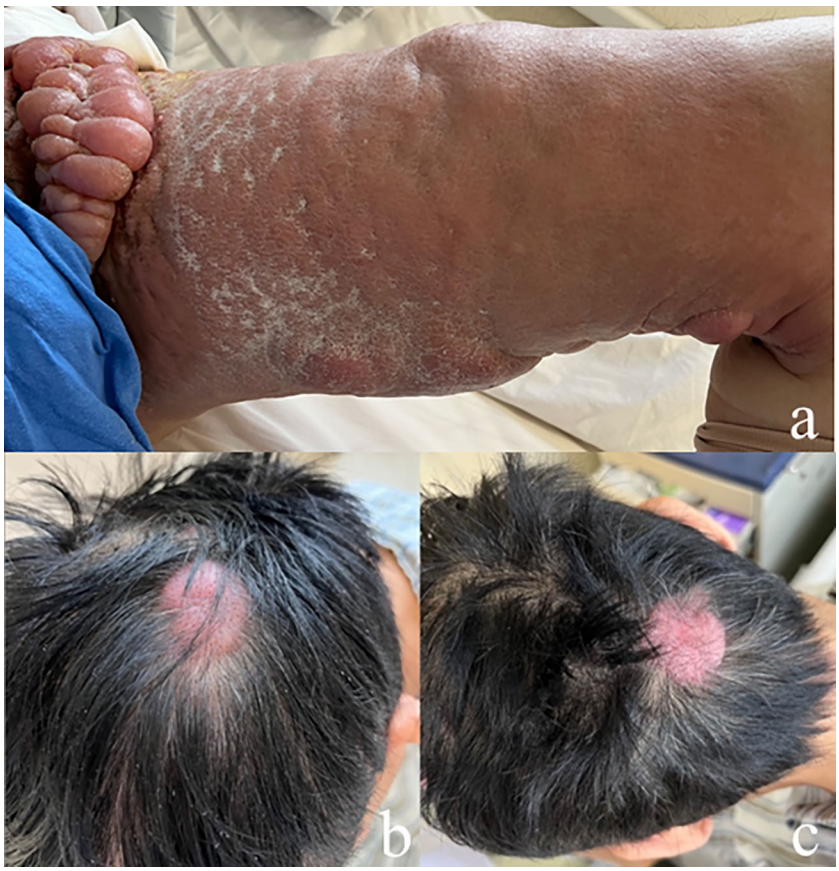

FIGURE 2
Cutaneous metastatic carcinomas. **(A)** Beaded mass in left groin area and erythematous scleroderma of the left thigh; **(B, C)** Two fleshy masses on the scalp.

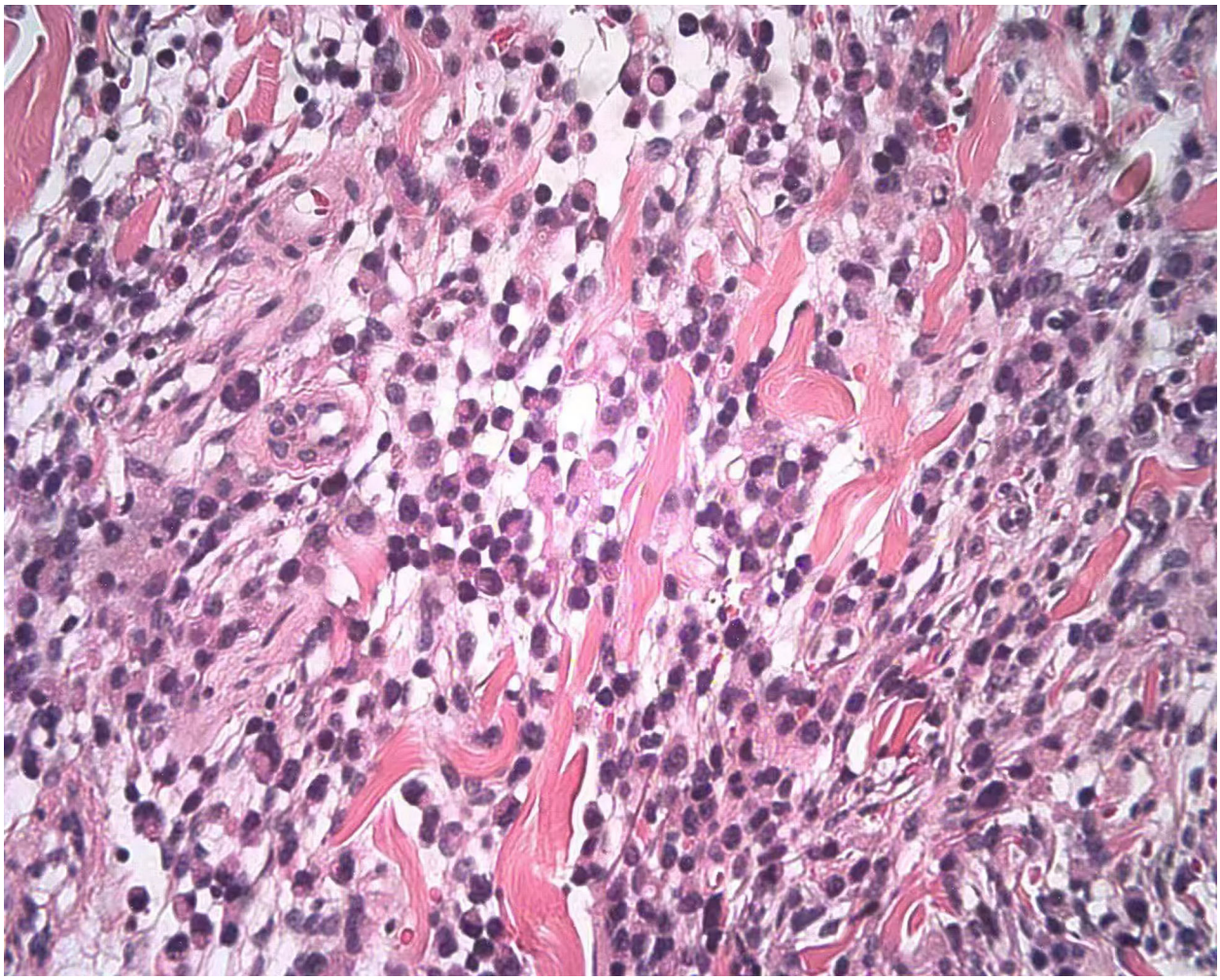

FIGURE 3
Skin biopsy of the groin mass; the pathology showed metastatic poorly differentiated carcinoma, some of which were signet-ring cell carcinoma.

many large hospitals in China, his symptoms were not alleviated. The diagnosis was not confirmed until a skin biopsy was performed half a year later; so, the best treatment opportunity was missed.

The pathogenesis of cutaneous metastases is still unclear. According to previous observations, poorly differentiated adenocarcinomas with signet-ring cell characteristics are closely related to the occurrence of cutaneous metastases. The proportion of SRC is inversely related to aggressive behavior, higher risk of metastases and poor prognosis in mixed-type gastric cancer (6). Some of the potential mechanisms are hematogenous or lymphatic metastasis. Holmgren L proposed the concept of "tumor dormancy" (7), as the reason for delayed skin metastases in gastric cancer, which refers to the state of small residual lesions or isolated micrometastases without causing symptoms for a long period of time (8). However, the triggers that activate dormant cells to lead to relapse have not been identified. In this case, the patient showed advanced recurrence of stage IIB gastric cancer, histopathology of the primary tumor was pT1 and N3, and the patient received only two adjuvant chemotherapy sessions after surgery. If an adequate course of adjuvant chemotherapy is given, it may reduce the risk of cancer recurrence.

Cutaneous metastasis of gastric cancer is one of the markers of an advanced tumor stage, suggesting a poor prognosis for patients, but about 61% of patients still receive active treatment with surgery, chemotherapy, or radiation therapy (9). Although the application of active treatment can significantly improve prognosis, there are many patients did not tolerate chemotherapy which likely increased their recurrence risk of disease. A new study analyzed the molecular profiling of signet-ring cell carcinoma (SRCC) from the stomach and colon by using NGS, immunohistochemistry and *in situ* hybridization, suggest that SRCCS harbor a similar molecular profile, regardless of the tumor location, means tailored therapy may become available for these patients in the future (10). Liu Shuzhen et al. reported 51 cases of skin metastases of malignant tumors; of these, 8 patients did not receive active antitumor treatment and died within 4 months (11). Among the 43 patients who received treatment, the median survival time was significantly longer than untreated patients, indicating that active treatment can prolong the survival of patients with skin metastases of malignant tumors, especially those without vital organ metastases.

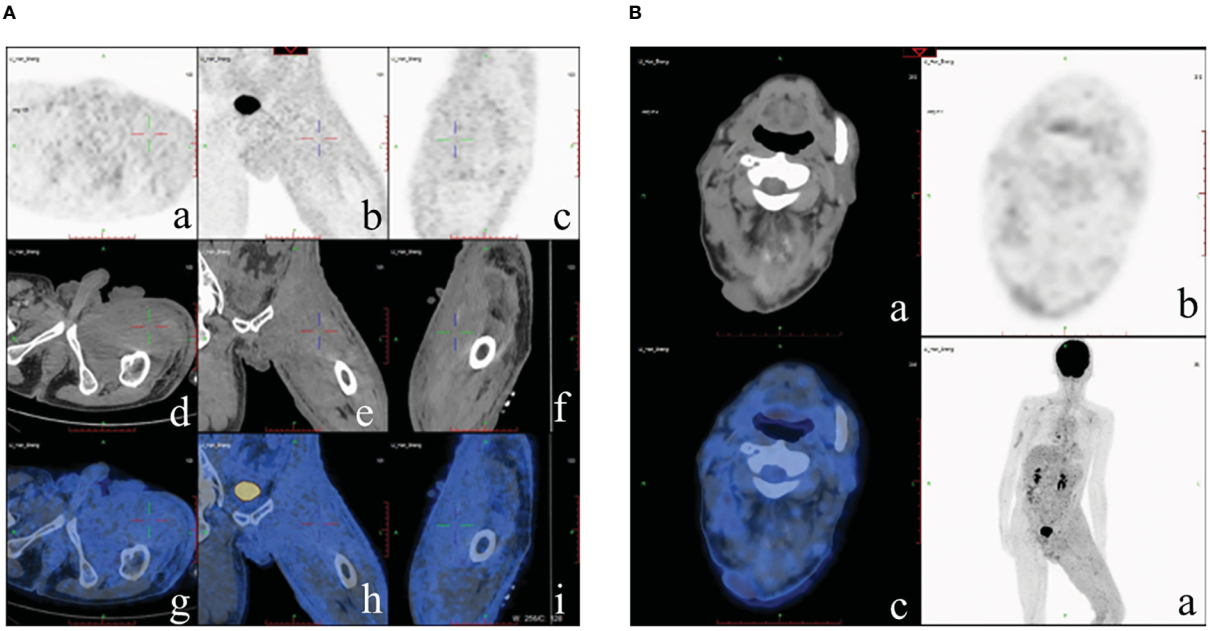

FIGURE 4
PET-CT examination. **(A)** Multiple humus-like hypodense nodules on the skin surface from the left groin to the thigh, secondary lymphedema, and slightly increased metabolic diffusion; **(B)** Localized thickening of the skin on the top of the left head and back of the neck and slightly increased metabolism.

Consequently, Signet-ring cell gastric cancer has a higher incidence of long-term cutaneous metastasis than other types of gastric cancer, and the possibility of tumor recurrence and metastasis should be highly suspected when skin lesions appear in patients with a clinical history of gastric cancer. Therefore, early diagnosis and treatment is extremely important. At the same time, multidisciplinary consultation and close cooperation between surgeons, oncologists, and dermatologists are of great significance to the diagnosis and treatment of this disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Author contributions

QL and YL made substantial contributions to design the research work. SY and PZ made substantial contributions to collecting the clinical data. SY and PZ wrote the initial draft of the manuscript. QL and YL revised the paper for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Anju Kumari,
Center for Cancer Research (NIH), United States
Gang Wang,
Cornell University, United States
Tong Wu,
Indiana University–Purdue University Indianapolis, United States

*CORRESPONDENCE
Tilman Bostel
tilman.bostel@unimedizin-mainz.de

†These authors have contributed equally to this work and share first authorship

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Chemoradiotherapy in geriatric patients with squamous cell carcinoma of the esophagus: Multi-center analysis on the value of standard treatment in the elderly

Tilman Bostel[1,2*†], Sati Akbaba[1,2†], Daniel Wollschläger[2,3†], Arnulf Mayer[1,2], Eirini Nikolaidou[1,2], Markus Murnik[4,5], Simon Kirste[4,5], Alexander Rühle[4,5], Anca-Ligia Grosu[4,5], Jürgen Debus[6,7], Christian Fottner[2,8], Markus Moehler[2,8], Peter Grimminger[2,9], Heinz Schmidberger[1,2] and Nils Henrik Nicolay[4,5,10]

[1]Department of Radiation Oncology, University Medical Center Mainz, Mainz, Germany, [2]German Cancer Consortium (Deutsches Konsortium fur Translationale Krebsforschung - DKTK) Partner Site Mainz, German Cancer Research Center (Deutsches Krebsforschungszentrum - DKFZ), Heidelberg, Germany, [3]Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Mainz, Germany, [4]Department of Radiation Oncology, University of Freiburg – Medical Center, Freiburg, Germany, [5]German Cancer Consortium (Deutsches Konsortium fur Translationale Krebsforschung - DKTK) Partner Site Freiburg, German Cancer Research Center (Deutsches Krebsforschungszentrum - DKFZ), Heidelberg, Germany, [6]Department of Radiation Oncology, University Hospital of Heidelberg, Heidelberg, Germany, [7]German Cancer Consortium (Deutsches Konsortium fur Translationale Krebsforschung - DKTK) Partner Site Heidelberg, German Cancer Research Center (Deutsches Krebsforschungszentrum - DKFZ), Heidelberg, Germany, [8]Department of Internal Medicine I, University Medical Center Mainz, Mainz, Germany, [9]Department of General, Visceral and Transplant Surgery, University Medical Center Mainz, Mainz, Germany, [10]Department of Radiation Oncology, University of Leipzig Medical Center, Leipzig, Germany

Background and purpose: To evaluate the tolerability and outcomes of chemoradiation in elderly patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Materials and methods: This multi-center retrospective analysis included 161 patients with SCC of the esophagus with a median age of 73 years (range 65-89 years) treated with definitive or neoadjuvant (chemo)radiotherapy between 2010 and 2019 at 3 large comprehensive cancer centers in Germany. Locoregional control (LRC), progression-free survival (PFS), distant metastasis-free survival (DMFS), overall survival (OS), and treatment-associated toxicities were analyzed, and parameters determining patient outcomes and treatment tolerance were assessed.

Results: The delivery of radiotherapy without dose reduction was possible in 149 patients (93%). In 134 patients (83%), concomitant chemotherapy was initially prescribed; however, during the course of therapy, 41% of these patients (n = 55) required chemotherapy de-escalation due to treatment-related toxicities. Fifty-two patients (32%) experienced higher-grade acute toxicities, and 22 patients (14%) higher-grade late toxicities. The 2-year LRC, DMFS, PFS, and OS rates amounted to

67.5%, 33.8%, 31.4%, and 40.4%, respectively. Upon multivariate analysis, full-dose concomitant chemotherapy (vs. no or modified chemotherapy) was associated with significantly better DMFS (p=0.005), PFS (p=0.005) and OS (p=0.001). Furthermore, neoadjuvant chemoradiotherapy followed by tumor resection (vs. definitive chemoradiotherapy or definitive radiotherapy alone) significantly improved PFS (p=0.043) and OS (p=0.049). We could not identify any clinico-pathological factor that was significantly associated with LRC. Furthermore, definitive (chemo) radiotherapy, brachytherapy boost and stent implantation were significantly associated with higher-grade acute toxicities (p<0.001, p=0.002 and p=0.04, respectively). The incidence of higher-grade late toxicities was also significantly associated with the choice of therapy, with a higher risk for late toxicities when treatment was switched from neoadjuvant to definitive (chemo)radiotherapy compared to primary definitive (chemo)radiotherapy (p<0.001).

Conclusions: Chemoradiation with full-dose and unmodified concurrent chemotherapy has a favorable prognostic impact in elderly ESCC patients; however, about half of the analyzed patients required omission or adjustment of chemotherapy due to comorbidities or toxicities. Therefore, the identification of potential predictive factors for safe administration of concurrent chemotherapy in elderly ESCC patients requires further exploration to optimize treatment in this vulnerable patient cohort.

KEYWORDS

esophageal cancer, elderly patients, squamous cell cancer, chemoradiation, radiotherapy

Introduction

Esophageal cancer is one of the most common cancers worldwide with over 470,000 new cases per year with a rapidly rising incidence (1, 2). Globally, most esophageal cancers are squamous cell carcinomas (ESCC) due to the widespread prevalence of risk factors. Despite all the advances in treatment in recent years, esophageal cancer remains one of the deadliest cancers globally due to an early lymphatic and vascular dissemination of tumor cells, with very poor 5-year survival rates ranging from 15-25% (2).

Increased age at diagnosis and an increasing life expectancy of the population in Western countries pose a problem for the treatment of esophageal cancer in the elderly, as treatment choices are governed by comorbidities, patient performance status and patient priorities (3, 4). In many landmark trials defining the role of chemoradiation in esophageal cancer, older patients have been underrepresented or excluded, making extrapolation of trial data to the elderly population problematic (5, 6). To date, there is no internationally consented definition of elderly patients; however, most studies define an age between 60 to 70 years as the minimum age for the classification of the elderly. For many elderly patients with esophageal cancers not suitable for surgical treatment, definitive radiotherapy with or without concomitant chemotherapy remains the curative treatment of choice. Despite the demonstrated benefits of adding chemotherapy to radiotherapy, concomitant chemoradiotherapy can result in severe adverse effects, especially in case of comorbidities or poor performance status prior to treatment initiation (7).

To date, there are only few datasets available that investigated the benefit of standard chemoradiotherapy for the treatment of esophageal cancers in the elderly (7–9). Our study aimed to analyze toxicity profiles and oncologic outcomes in a large multi-center cohort of elderly ESCC patients treated with neoadjuvant or definitive (chemo)radiotherapy. We also investigated potential prognostic factors associated with an adverse treatment response and the occurrence of higher-grade toxicities in order to guide treatment decisions in this vulnerable patient population.

Material and methods

Patients

In this retrospective multi-center study, patients with histologically confirmed ESCC and a minimum age of 65 years without distant metastasis at initial diagnosis were included. Patients were treated with either chemoradiotherapy or radiotherapy at the University Hospitals of Mainz, Freiburg, and Heidelberg from 2000 to 2019. Demographic, clinical and pathological data were obtained from electronic medical records, pathology reports and the cancer registries of participating centers. Staging of esophageal carcinomas was based on the versions of the TNM classification (Union for International Cancer Control [UICC]) and the clinical stages of the American Joint Committee on Cancer

(AJCC) that were current at the time of first diagnosis (i.e., 6th, 7th or 8th edition of the UICC-AJCC TNM classification). This analysis has been approved by the independent ethics committees of the medical faculties of the universities of Mainz (no reference number), Freiburg (reference no. 275/18) and Heidelberg (reference no. S-040/2018).

Treatment groups

The majority of patients were treated for locally advanced tumors and received either neoadjuvant chemoradiotherapy followed by surgery or definitive (chemo)radiotherapy. Treatment decisions were based on multidisciplinary tumor board recommendations. Radiation planning was performed with either conventional 3D conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT).

A total of 61 patients received (chemo)radiation in neoadjuvant intention with a median total dose of 41.4 Gy (range 40.0 - 56.0 Gy) and median single doses of 1.8 Gy (range 1.8 - 2.0 Gy). Only four of the preoperatively treated patients received sequential dose escalation to the macroscopic tumor by either teletherapy (n = 3, cumulative doses of 50.4 - 54 Gy, single doses 1.8 - 2.1 Gy) or brachytherapy (n = 1, cumulative dose of 54 Gy, single dose 4.0 Gy). One patient underwent additional postoperative irradiation due to incomplete tumor resection (R1 situation) with a cumulative dose of 66 Gy. In 8 patients, neoadjuvant chemoradiotherapy was not followed by surgery because of treatment-related deterioration of patient performance status (n = 2), patient refusal to undergo surgery after completion of neoadjuvant therapy (n = 4), comorbidities (n = 1) or newly diagnosed liver metastases upon intermediate staging prior to surgery (n = 1). In addition, 11 patients switched from the planned neoadjuvant chemoradiation to a definitive treatment regimen by increasing the doses of both radiotherapy and chemotherapy because of patient refusal to undergo surgery (n = 1), irresectability (n = 6), comorbidities (n = 2) and for unknown reasons (n = 2). In our analysis, we assigned all those patients with initial neoadjuvant therapy and no subsequent surgery to the definitive (chemo) radiation group. Neoadjuvant chemoradiotherapy concepts applied until 2012 differed between participating centers (see Supplementary Table S1). From 2013 onwards, neoadjuvant treatments were performed according to the protocol of the CROSS trial at all participating centers. The CROSS regimen comprises radiotherapy up to a total dose of 41.4 Gy using single doses of 1.8 Gy and concurrent application of paclitaxel (50 mg/m^2) and carboplatin (AUC of 2 mg/ml/min) on days 1, 8, 15, 22 and 29 (n = 19 patients) (6).

Definitive (chemo)radiotherapy was administered to 119 patients. Primary tumors and affected lymph nodes including a safety margin (*see below*) and the regional lymphatic drainage area (elective) were treated to a median total dose of 50 Gy (range 12.6 - 73.8 Gy) using median single doses of 1.8 Gy (range 1.6 - 2.5 Gy). The majority of patients (n = 86, 72%) received dose escalation to the macroscopic tumor tissue by using simultaneous integrated or sequential teletherapy boost (median total dose 9.0, range 4.0 - 27.0 Gy; median single dose 2.0 Gy, range 1.8 - 3.0 Gy; n = 78, 66%) and/or brachytherapy boost (median total dose 8.0, range 4.0 - 24.0 Gy; median single dose 4.0 Gy, range 4.0 - 6.0 Gy; n = 24, 20%). The median cumulative dose was 58.8 Gy (range 12.6 - 74.0 Gy). Different chemotherapy regimens were applied in combination with definitive radiotherapy, as outlined in Supplementary Table S2.

The fitness of patients to receive radiotherapy and concomitant chemotherapy was assessed at baseline. Reasons for discontinuation or reduction of radiotherapy and concomitant chemotherapy were obtained from patient files. For this analysis, we defined combinations of a platinum derivate and 5-fluorouracil (5-FU), carboplatin and paclitaxel, mitomycin C and 5-FU and FOLFOX as standard chemotherapy regimens. Other chemotherapy regimens such as monotherapy with 5-FU, Capecitabine or a platinum compound alone or dose reduction of chemotherapy during radiation treatment were defined as a modification of chemotherapy. Moreover, we defined full-dose radiotherapy and full-dose chemotherapy as administration of both treatment modalities without interruption, dose reduction or modification.

Target volume definition

The primary gross tumor volume (GTV) and lymph node GTV(s) were defined based on planning computed tomography (CT) and staging examinations including contrast-enhanced CT, PET/CT, endosonography, and endoscopic clip markings of the oral and aboral tumor margins, if available. The clinical target volume (CTV) was generated by adding a safety margin of 3 - 5 cm in the oral and aboral directions and 1 - 2 cm in the axial direction to the GTV of the primary tumor and 1 cm safety margin to the GTV of the lymph node metastasis. Regional elective lymphatic drainage was regularly included in the CTV. Adjustment of the CTV to anatomical barriers such as the bone, lungs, or heart and to the stomach was performed in case of distal cancers. The planning target volume (PTV) included the CTV and an additional craniocaudal and lateral safety margin of 0.5 - 1.0 cm. Boost volumes were obtained by expanding the primary GTV by 2 cm craniocaudally and 1 - 2 cm circumferentially, and the lymph node GTV(s) by 0.5 - 1 cm in all directions.

Oncologic outcomes and toxicity

All patients received regular follow-up examinations at 3- to 6-month intervals, including clinical examinations as well as multi-region CT imaging. In case of suspected locoregional or distant tumor recurrence on CT, additional diagnostic work-up was performed. Locoregional control (LRC) was defined as the time from the end of radiotherapy without progression of the primary tumor and without evidence of new-onset or progressive locoregional lymph node metastases. Distant metastasis-free survival (DMFS) was defined as the time from the end of radiotherapy to the new onset of distant metastases or death from any cause. Overall survival (OS) was defined as the time from the end of radiotherapy to death from any cause. Progression-free survival (PFS) was defined as the time from the end of radiotherapy to progression of tumor disease of any site or death from any cause. Missing survival data were obtained from the cancer registries. Acute and chronic adverse events were classified according to the CTCAE criteria version 5.0.

Statistical analysis

Statistical analysis was performed using R software, version 4.1.3 (R Core Team 2022, Vienna, Austria). P-values of $p<0.05$ were considered statistically significant. The Kaplan-Meier method was used to estimate survival after radiotherapy, with the log-rank test to determine statistical significance. Moreover, multivariable analyses were performed using the Cox proportional hazards model and associated Wald tests to identify predictors of LRC, DMFS, PFS, and OS after radiotherapy. Since chemotherapy was sometimes completed after the end of radiotherapy, tests involving completion of chemotherapy as a predictor were based on a Cox model with time-varying covariates to avoid immortal-time bias.

Results

Patient and treatment characteristics

A total of 161 patients with histologically confirmed SCC of the esophagus were included in this retrospective multi-center analysis. Patients were predominantly male (n = 119, 74%) and had a median age of 73 years (range 65 to 89 years). According to the consensus definition of the United States National Institute of Aging, the study population was subdivided into the following 3 age groups: "young olds" (65 to 74 years), "older olds" (75 to 84 years) and "oldest olds" (≥ 85 years) (10). In our study population, the majority of patients belonged to the "young old" subgroup (n = 96, 60%), whereas the proportion of patients classified as "older old" and "oldest old" amounted to 37% (n = 59) and 4% (n = 6), respectively. The majority of analyzed patients exhibited a relatively good performance status prior to treatment, with 133 patients (83%) having Eastern Cooperative Oncology Group (ECOG) values in the range of 0 to 1. Most tumors were located in the thoracic portion of the esophagus (n = 142, 88%), and 37% (n = 59) of cancers were localized in the mid-thoracic segment (24 to 32 cm from dentition) with a median tumor length of 5 cm (range 1 - 13 cm). The majority of patients suffered from locally advanced disease at diagnosis with 134 patients (83%) having cT3/4 tumors and 119 patients (74%) exhibiting lymphogenic tumor spread on imaging or endosonography. The majority of SCC were moderately or poorly differentiated (55% and 31%, respectively).

Forty-two patients (26%) received neoadjuvant radiotherapy of whom 19 (45%) were treated with carboplatin and paclitaxel, and 23 patients (55%) with cisplatin and 5-FU. No patient had to prematurely discontinue neoadjuvant radiotherapy. Concomitant chemotherapy was reduced or modified in 12 of these patients (29%) due to deteriorating performance status or acute toxicities. Overall, more than 80% of the initially prescribed chemotherapy dose could be applied in 35 of the patients receiving neoadjuvant treatment (83%).

One hundred and nineteen patients (74%) were treated with definitive radiotherapy, of whom 92 patients (77%) received concurrent chemoradiotherapy and 4 patients (3%) received a concomitant EGFR receptor antibody (cetuximab). Various concurrent chemotherapy regimens were administered in the definitive treatment situation, including cisplatin/5-FU (n = 59, 50%), carboplatin/5-FU (n = 4, 3%), carboplatin/paclitaxel (n = 10, 8%), FOLFOX (n = 9, 8%), mitomycin C and 5-FU (n = 2, 2%), 5-FU or Capecitabine alone (n = 6, 5%), or a platinum derivative alone (n = 2, 2%). One hundred and seven patients (90%) received full dose definitive radiotherapy, and only 60 patients (50%) completed concomitant chemotherapy as initially prescribed. The reasons for premature discontinuation of radiotherapy were acute toxicities and deterioration of general condition (n = 8; 7%), patient request (n = 1, 1%), or death during treatment (n = 3; 3%), while chemotherapy dose was reduced due to treatment-related toxicities. The full treatment regimen of definitive chemoradiation including all concomitant and adjuvant chemotherapy cycles could only be administered to 49 patients (41%) due to treatment-related toxicities. In 74 patients (62%), more than 80% of initially prescribed chemotherapy dose was applied in the definitive treatment situation.

Overall, 48 patients (30%) underwent bougienage due to malignant stenosis of the esophagus and 29 patients (18%) underwent stent implantation.

Detailed information on tumor and patient characteristics are listed in Table 1.

Treatment outcome

Three patients died (2%) during radiotherapy due to sepsis (n = 2) or acute tumor bleeding (n = 1), respectively, and were therefore excluded from all further analyses regarding oncologic response. For the entire cohort, the 1-, 2- and 5-year LRC rates were 79.7% (95% CI 72.6% - 87.4%), 67.5% (95% CI 58.4% - 77.9%) and 54.7% (95% CI 44.2% - 67.7%), while the corresponding DMFS rates were 49.7% (95% CI 42.4% - 58.2%), 33.8% (95% CI 26.9% - 42.5%) and 15.9% (95% CI 10.2% - 24.8%), respectively. PFS after 1, 2 and 5 years amounted to 46.9% (95% CI 39.6% - 55.6%), 31.4% (95% CI 24.6% - 40.1%) and 15.5% (95% CI 9.7% - 24.6%), and OS to 58.2% (95% CI 50.9%-66.4%), 40.4% (95% CI 33.2%-49.1%) and 17.3% (95% CI 11.4%-26.3%) at the respective time points. The recurrence patterns are summarized in detail in Supplementary Table S3.

Better OS was significantly associated with patient performance status (ECOG 1-2 vs. 3-4: p=0.001, log-rank test), administration of full-dose systemic therapy (vs. no or reduced systemic therapy doses; $p<0.001$, univariate Cox model) and neoadjuvant chemoradiation followed by surgery (vs. other treatments; p=0.002, log-rank test) (see Table 2A and Figures 1–3). For radiotherapy adherence (complete vs. incomplete administration), there was also a statistically significant OS difference after radiotherapy (p=0.01, log-rank test; 2-year OS 42.0% vs. 18.8%). Age, gender, comorbidities (Charlson Comorbidity Index), tumor extension (T stage), metastatic nodal spread (N stage), tumor stage according to the Union for International Cancer Control (UICC), and localization of the primary tumor were not significantly associated with OS (see Table 2A).

In multivariate analysis, neoadjuvant chemoradiotherapy followed by tumor resection and administration of concomitant non-modified chemotherapy remained significantly associated with better PFS and OS (2-year PFS 21.2% vs. 9.5%, HR 0.55, 95% CI 0.36 - 0.83, p=0.005; 2-year OS 48% vs. 15%; HR 0.51, 95% CI 0.34 - 0.77, p=0.001), while DMFS was only significantly associated with fully administered unmodified chemotherapy (see Tables 2A–C and

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TABLE 1 Tumor and patient characteristics at baseline.

Variable	Value	n	%
Gender	male	119	73.9
	female	42	26.1
Age	65-74 years	96	59.6
	75-84 years	59	36.7
	≥ 85 years	6	3.7
ECOG	0	58	36.0
	1	75	46.6
	2	28	17.4
Localization (distance from incisors)	Cervical (15 - 18 cm)	19	11.8
	Upper thoracic (18 - 24 cm)	42	26.1
	Middle thoracic (24 - 32 cm)	59	36.7
	Lower thoracic (32 - approximate 40 cm)	41	25.5
cT-stage	T1	6	3.7
	T2	19	11.8
	T3	101	62.7
	T4	33	20.5
	Tx	2	1.2
cN-stage	N0	40	24.8
	N+	119	73.9
	Nx	2	1.2
M-stage	M0	161	100.0
	M1	0	0
AJCC-stage	1	4	2.5
	2	39	24.2
	3	81	50.3
	4a	34	21.1
	NA	3	1.9
Grading	G1	3	1.9
	G2	92	57.1
	G3	48	29.8
	G4	0	0
	Gx	18	11.2
Charlson Comorbidity Index	≤ 5	64	39.8
	> 5	95	59.0
	NA	2	1.2

Staging of esophageal carcinomas was based on the versions of the TNM classification (Union for International Cancer Control [UICC]) and the clinical stages of the American Joint Committee on Cancer (AJCC) that were current at the time of first diagnosis (i.e., 6^{th}, 7^{th} or 8^{th} edition of the UICC-AJCC TNM classification).
ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer.

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TABLE 2A Univariate analyses of potential prognostic factors for overall survival (OS).

Factors	OS at 1 year (%)	OS at 2 years (%)	OS at 5 years (%)	p - value
Age				
65 - 74 years	61	47	25	
75 – 84 years	56	33	4	
≥ 85 years	40	–	–	0.08
Gender				
Female	61	32	13	
Male	57	43	19	0.60
ECOG score				
0 - 1	63	45	20	
2 - 3	33	21	–	**0.001**
Charlson Comorbidity Index				
≤ 5	59	40	24	
> 5	57	41	11	0.20
Clinical tumor classification (cT)				
1	67	50	–	
2	68	50	9	
3	56	40	20	
4	58	37	22	0.90
Clinical lymph node classification (cN)				
Nodal negative (N0)	48	35	11	
Nodal positive (N+)	62	43	21	0.10
Tumor stage (AJCC)				
1 - 2	53	36	9	
3	59	45	20	
4a	63	41	26	0.70
Localization of the primary tumor				
0 - 18 cm distance from the incisors (cervical)	68	51	24	
18 - 24 cm distance from the incisors (upper thoracic third)	66	49	25	
24 - 32 cm distance from the incisors (middle thoracic third)	58	32	11	
32 - 40 cm distance from the incisors (lower thoracic third)	46	38	22	0.60
Administration of full-dose RT				
yes	60	42	18	
no	28	19	–	**0.01**
Cumulative dose of RT (EQD2)				
≤ 50 Gy	57	42	21	
> 50 Gy	59	39	14	0.90
Administration of non-modified, full-dose chemotherapy				
yes	76	58	30	
no	43	24	7	< **0.001**

(Continued)

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TABLE 2A Continued

Factors	OS at 1 year (%)	OS at 2 years (%)	OS at 5 years (%)	p - value
Treatment concept				
Neoadjuvant CRT followed by surgical resection	71	58	41	
Definitive RT/CRT	54	34	9	**0.002**

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; RT, radiotherapy; EQD2, equivalent dose in 2 Gy fractions; CRT, chemoradiotherapy. Bold values, significant p-values.

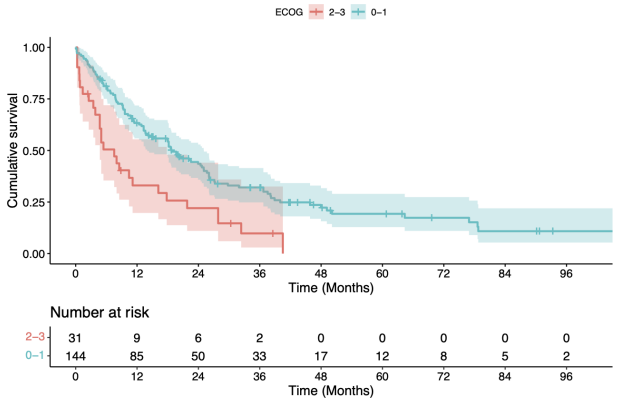

FIGURE 1
Kaplan-Meier estimate of overall survival (OS) after radiotherapy stratified by Eastern Cooperative Oncology Group (ECOG) Performance Score 0 - 1 vs. 2 - 3. OS was significantly better for patients with an ECOG of ≤ 1 (p = 0.001, log-rank test).

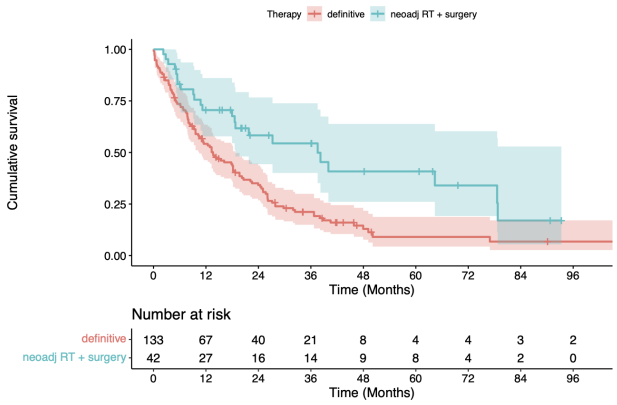

FIGURE 2
Kaplan-Meier estimate of overall survival (OS) after radiotherapy stratified by scheduled application of chemotherapy vs. no or modified administration of chemotherapy. OS was significantly better for patients with a scheduled application of chemotherapy (p < 0.001, log-rank test).

Tables 3A–C). In contrast, none of the factors analyzed was statistically significantly associated with LRC (see Tables 2D, 3D).

Treatment-related toxicities

In our study population, 51 patients (32%) developed severe or life-threatening acute toxicities (CTCAE grade 3/4) during (chemo) radiation, with hematologic side effects, new-onset or progressive dysphagia with consecutive weight loss and increasing esophageal stenosis being the most common adverse events. Acute grade 5 toxicities with lethal outcome were observed in 3 patients (2%).

Higher-grade late toxicities (CTCAE grade 3/4) were diagnosed in 22 patients (14%), with dysphagia and/or new-onset or increasing stenosis of the esophagus as the most prevalent adverse events that required further interventions. Two patients (1%) developed late grade 5 toxicities with ulceration in the anastomotic area, recurrent bleeding and fatal outcome. The detailed toxicity profile of radiation or chemoradiation treatment is summarized in Table 4. In our analysis, acute toxicity was significantly associated with the type of therapy, with neoadjuvant chemoradiotherapy associated with a lower chance for the occurrence of severe acute toxicity than definitive (chemo)radiotherapy (p<0.001; see Supplementary Table S4). In addition, brachytherapy boost and stent implantation were associated with a higher risk for severe acute toxicities. Other factors such as age and sex, performance status, comorbidities, location or length extent of the primary tumor, T or N stage, UICC stage, or administration of concurrent chemotherapy without dose reduction were not statistically significantly associated with the occurrence of severe acute toxicities (see Supplementary Table S4).

The incidence of severe late toxicities was also significantly associated with the type of therapy, with a higher chance of late toxicities when there was a switch in the treatment concept from neoadjuvant to definitive (chemo)radiotherapy compared with primary definitive (chemo)radiotherapy (p< 0.001), while no statistically significant association was found for the age, sex, comorbidities, localization of the primary tumor, N stage, stent implantation, brachytherapy, and chemotherapy without dose reduction (see Supplementary Table 5).

Discussion

Our analysis demonstrated very good tolerability of radiotherapy in elderly esophageal squamous cell cancer patients. However, only about half of patients in our cohort could receive concomitant chemotherapy without dose reduction or modification due to comorbidities and toxicities. Upon multivariate analysis, neoadjuvant chemoradiotherapy followed by tumor resection and concomitant non-modified chemotherapy was found to be the key factor determining better PFS and OS in elderly ESCC patients.

In general, therapeutic decisions in the treatment of elderly cancer patients depend to a considerable extent on patient-individual factors such as patient performance, comorbidities, and chronological age of patients. Many studies have shown that age-related modifications of standard therapy in general influence treatment response of various cancers (11, 12).

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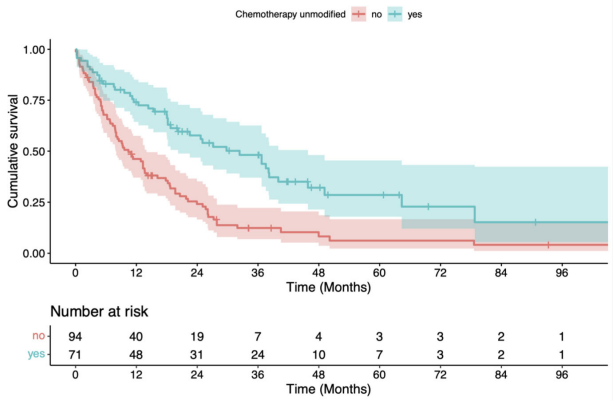

FIGURE 3
Kaplan-Meier estimate of overall survival (OS) after radiotherapy stratified by neoadjuvant chemoradiation followed by surgical resection vs. definitive treatment with (chemo)radiation. OS was significantly better for patients who received neoadjuvant treatment (p = 0.002, log-rank test).

However, despite the high clinical importance, available data for esophageal cancer therapy in the elderly are mainly derived from retrospective studies except for one recent prospective randomized study that reported survival of elderly esophageal cancer patients after chemoradiotherapy with S-1 or radiotherapy alone (8, 9, 13–17). Most reports analyzed elderly esophageal cancer patients with both adenocarcinomas and SCCs, and most of these studies have demonstrated a survival benefit for additional concomitant chemotherapy, including the only published prospective study to date with an exclusively elderly patient population (9). For example, in a large retrospective analysis of the SEER database, 3020 elderly patients (≥ 65 years) with esophageal cancers treated with chemoradiation or radiotherapy alone were analyzed. In this analysis, the five-year overall and cancer-specific survival rates were only 13% and 20%, respectively; comparing the treatment modalities by propensity-score matching, a significant survival benefit of chemoradiotherapy versus radiotherapy was evident regardless of patient age (8). Other retrospective studies of elderly patients with esophageal cancer reported 5-year OS rates in the range of 5 - 36% after (chemo)radiotherapy (17, 18).

TABLE 2B Univariate analyses of potential prognostic factors for progression-free survival (PFS).

Factors	PFS at 1 year (%)	PFS at 2 years (%)	PFS at 5 years (%)	p - value
Age				
65 – 74 years	57	37	20	
75 – 84 years	54	32	9	
≥ 85 years	21	–	–	0.08
Gender				
Female	54	26	12	
Male	55	37	16	0.60
ECOG score				
0 - 1	58	35	17	
2 - 3	37	26	6	0.06
Charlson Comorbidity Index				
≤ 5	59	39	25	
> 5	50	29	6	0.05
Clinical tumor classification (cT)				
1	67	67	25	
2	53	32	8	
3	53	34	16	
4	59	32	22	1.00
Clinical lymph node classification (cN)				
Nodal negative (N0)	50	31	14	
Nodal positive (N+)	56	35	16	0.50
Tumor stage (AJCC)				
1 - 2	46	27	12	
3	56	38	14	

(Continued)

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TABLE 2B Continued

Factors	PFS at 1 year (%)	PFS at 2 years (%)	PFS at 5 years (%)	p - value
4a	61	34	26	0.50
Localization of the primary tumor				
0 - 18 cm distance from the incisors (cervical)	52	34	15	
18 - 24 cm distance from the incisors (upper thoracic third)	67	44	23	
24 - 32 cm distance from the incisors (middle thoracic third)	54	30	9	
32 - 40 cm distance from the incisors (lower thoracic third)	44	29	19	0.80
Administration of full-dose RT				
yes	55	35	17	
no	45	11	–	**0.04**
Cumulative dose of RT (EQD2)				
≤ 50 Gy	55	35	18	
> 50 Gy	55	33	14	0.90
Administration of non-modified, full-dose chemotherapy				
yes	69	51	26	
no	40	19	8	0.47
Treatment concept				
Neoadjuvant CRT followed by surgical resection	71	55	36	
Definitive RT/CRT	49	27	8	< **0.001**

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; RT, radiotherapy; EQD2, equivalent dose in 2 Gy fractions; CRT, chemoradiotherapy. Bold values, significant p-values.

TABLE 2C Univariate analyses of potential prognostic factors for distant metastasis-free survival (DMFS).

Factors	DMFS at 1 year (%)	DMFS at 2 years (%)	DMFS at 5 years (%)	p - value
Age				
65 – 74 years	50	39	22	
75 – 84 years	51	28	6	
≥ 85 years	25	–	–	0.30
Gender				
Female	50	24	12	
Male	50	37	17	0.50
ECOG score				
0 - 1	54	36	18	
2 - 3	30	21	–	**0.003**
Charlson Comorbidity Index				
≤ 5	50	38	23	
> 5	48	31	9	0.20
Clinical tumor classification (cT)				
1	67	50	–	
2	47	34	9	
3	47	34	17	

(Continued)

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TABLE 2C Continued

Factors	DMFS at 1 year (%)	DMFS at 2 years (%)	DMFS at 5 years (%)	p - value
4	56	34	23	1.00
Clinical lymph node classification (cN)				
Nodal negative (N0)	39	30	10	
Nodal positive (N+)	54	36	19	0.1
Tumor stage (AJCC)				
1 - 2	38	25	8	
3	52	40	17	
4a	57	35	27	0.30
Localization of the primary tumor				
0 - 18 cm distance from the incisors (cervical)	53	41	15	
18 - 24 cm distance from the incisors (upper thoracic third)	63	40	27	
24 - 32 cm distance from the incisors (middle thoracic third)	49	30	9	
32 - 40 cm distance from the incisors (lower thoracic third)	36	30	20	0.80
Administration of full-dose RT				
yes	53	36	17	
no	9	–	–	< **0.001**
Cumulative dose of RT (EQD2)				
≤ 50 Gy	46	34	19	
> 50 Gy	53	34	14	0.90
Administration of non-modified, full-dose chemotherapy				
yes	67	51	27	
no	34	18	7	< **0.001**
Treatment concept				
Neoadjuvant CRT followed by surgical resection	61	55	36	
Definitive RT/CRT	46	27	9	**0.002**

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; RT, radiotherapy; EQD2, equivalent dose in 2 Gy fractions; CRT, chemoradiotherapy. Bold values, significant p-values.

TABLE 2D Univariate analyses of potential prognostic factors for locoregional control (LRC).

Factors	LRC at 1 year (%)	LRC at 2 years (%)	LRC at 5 years (%)	p - value
Age				
65 – 74 years	84	71	63	
75 – 84 years	76	64	40	
≥ 85 years	–	–	–	**0.03**
Gender				
Female	84	60	43	
Male	78	68	57	0.90
ECOG score				
0 - 1	82	70	58	
2 - 3	64	51	–	0.05

(Continued)

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TABLE 2D Continued

Factors	LRC at 1 year (%)	LRC at 2 years (%)	LRC at 5 years (%)	p - value
Charlson Comorbidity Index				
≤ 5	86	71	64	
> 5	75	65	46	0.20
Clinical tumor classification (cT)				
1	50	50	–	
2	79	79	68	
3	80	66	51	
4	86	66	66	0.20
Clinical lymph node classification (cN)				
Nodal negative (N0)	63	50	35	
Nodal positive (N+)	85	73	61	**0.009**
Tumor stage (AJCC)				
1 - 2	64	58	45	
3	87	71	54	
4a	82	71	71	0.20
Localization of the primary tumor				
0 - 18 cm distance from the incisors (cervical)	92	81	58	
18 - 24 cm distance from the incisors (upper thoracic third)	79	63	47	
24 - 32 cm distance from the incisors (middle thoracic third)	84	71	58	
32 - 40 cm distance from the incisors (lower thoracic third)	69	62	62	0.60
Administration of full-dose RT				
yes	80	69	56	
no	75	–	–	0.50
Cumulative dose of RT (EQD2)				
≤ 50 Gy	81	69	69	
> 50 Gy	79	67	46	0.20
Administration of non-modified, full-dose chemotherapy				
yes	88	79	67	
no	73	55	45	**0.02**
Treatment concept				
Neoadjuvant CRT followed by surgical resection	91	83	77	
Definitive RT/CRT	75	62	46	**0.009**

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; RT, radiotherapy; EQD2, equivalent dose in 2 Gy fractions; CRT, chemoradiotherapy. Bold values, significant p-values.

In this large multi-center cohort focusing on ESCC, we demonstrated that radiotherapy and chemoradiation are feasible treatment modalities for elderly esophageal cancer patients associated with relatively high rates of LRC (2- and 5-year LRC rates 67.5% and 54.7%, respectively). However, with a median PFS of 10.8 months, median DMFS of 11.6 months and median OS of only 18 months, the oncologic outcomes for this elderly patient population are considerably worse than for the highly selected younger cohorts of patients that have defined treatment standards based on several large randomized controlled trials in recent years (19, 20). For example, the recently published CheckMate 577 trial reported a disease-free survival of 22 months for patients with completely resected stage II or III cancers of the esophagus or gastroesophageal junction when patients received additional adjuvant treatment with nivolumab for pathologically incomplete remission after neoadjuvant chemoradiation (21). In contrast, several retrospective studies with large patient cohorts suggested that the OS among older patients might be comparable to that of

TABLE 3A Multivariate analysis of clinical parameters regarding overall survival (OS) of esophageal SCC in elderly patients after definitive or neoadjuvant CRT/RT.

Factors	HR	CI 95%	p-value
Age	1.003	0.965 - 1.042	0.892
ECOG score	1.537	0.946 - 2.497	0.083
Administration of full-dose RT	0.752	0.380 - 1.488	0.414
Administration of non-modified, full-dose chemotherapy	0.509	0.336 - 0.771	**0.001**
Neoadjuvant CRT followed by surgery vs. definitive RT/CRT	0.608	0.370 - 0.999	**0.049**

SCC, squamous cell carcinoma; CRT, chemoradiotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group. Bold values, significant p-values.

TABLE 3B Multivariate analysis of clinical parameters regarding progression-free survival (PFS) of esophageal SCC in elderly patients after definitive or neoadjuvant CRT/RT.

Factors	HR	CI 95%	p-value
Age	0.998	0.960 - 1.037	0.913
ECOG score	1.475	0.897 - 2.425	0.125
Administration of full-dose RT	0.832	0.386 - 1.793	0.639
Administration of non-modified, full-dose chemotherapy	0.548	0.361 - 0.831	**0.005**
Neoadjuvant CRT followed by surgery vs. definitive RT/CRT	0.597	0.362 - 0.983	**0.043**

SCC, squamous cell carcinoma; CRT, chemoradiotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group. Bold values, significant p-values.

TABLE 3C Multivariate analysis of clinical parameters regarding distant metastasis-free survival (DMFS) of esophageal SCC in elderly patients after definitive or neoadjuvant CRT/RT.

Factors	HR	CI 95%	p-value
Age	0.994	0.957 - 1.032	0.742
ECOG score	1.364	0.831 - 2.240	0.219
Administration of full-dose RT	0.596	0.303 - 1.172	0.134
Administration of non-modified, full-dose chemotherapy	0.544	0.357 - 0.829	**0.005**
Neoadjuvant CRT followed by surgery vs. definitive RT/CRT	0.621	0.376 - 1.025	0.063

SCC, squamous cell carcinoma; CRT, chemoradiotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index. Bold value, significant p-value.

TABLE 3D Multivariate analysis of clinical parameters regarding locoregional control (LRC) of esophageal SCC in elderly patients after definitive or neoadjuvant CRT/RT.

Factors	HR	CI 95%	p-value
Age	1.053	0.987 - 1.120	0.120
ECOG score	1.736	0.739 - 4.080	0.210
Administration of full-dose RT	1.014	0.226 - 4.540	0.990
Administration of non-modified, full-dose chemotherapy	0.569	0.279 - 1.160	0.120

SCC, squamous cell carcinoma; CRT, chemoradiotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group.

younger patients after multimodal treatment including surgery (14, 15). As the majority of patients in our analysis was classified as technically or conditionally unresectable, the oncologic outcomes in our study should be compared more with results from other trials in which definitive chemoradiation was applied. In this regard, several landmark trials of definitive chemoradiation in patients with ESCC reported comparable median OS rates ranging between 14 to 19 months (22–24).

In our analysis, unmodified administration of chemotherapy in combination with radiation and neoadjuvant chemoradiotherapy followed by surgery were found to be significant prognosticators for PFS and OS. In addition, administration of standard

TABLE 4 Acute and late severe and life-threatening toxicities (grade 3 and 4 according to CTCAE v5.0) of (chemo)radiotherapy in elderly patients with SCC of the esophagus.

Variable	Value
Acute toxicities – no. (%)	51 (31.7)
- Hematological side effects – no. (%)	27 (16.8)
- Dysphagia – no. (%)	27 (16.8)
- Esophageal stenosis – no. (%)	9 (5.6)
- Mucositis/odynophagia – no. (%)	10 (6.2)
- Acute renal failure – no. (%)	2 (1.2)
- Tumor bleeding – no. (%)	4 (2.5)
- Fistula – no. (%)	1 (0.6)
- Pneumonia – no. (%)	2 (1.2)
- Perforation and mediastinitis – no. (%)	1 (0.6)
- Pulmonary artery embolism – no. (%)	2 (1.2)
- Damage to the vestibular organ – no. (%)	1 (0.6)
- Radiation dermatitis – no. (%)	1 (0.6)
Late toxicities – no. (%)	22 (13.7)
- Dysphagia – no. (%)	19 (11.8)
- Esophageal stenosis – no. (%)	18 (11.2)
- Ulcera with tumor bleeding and lethal outcome – no. (%)	2 (1.2)
- Diarrhea – no. (%)	1 (0.6)

chemoradiotherapy without dose reduction resulted in improved DMFS, whereas none of the analyzed clinico-pathological factors had a statistically significant impact on LRC. Similarly to our previous trials, we could not demonstrate age- or comorbidity-related differences in terms of outcome (25–28).

Several other recently published analyses with exclusively elderly patients also demonstrated the prognostic value of concomitant chemoradiation without dose reduction of chemotherapy (8, 9, 13, 16, 17, 29). However, there are also a few retrospective studies using propensity score matching that have reported no benefit of concomitant chemoradiation in elderly patients with esophageal cancer (30) or have demonstrated a benefit of chemoradiation only for patients with cT4 tumors, absence of nodal involvement (cN0), or diabetes (18). Given these conflicting results, further large multi-center analyses are needed to clarify the role of concomitant chemoradiation in elderly esophageal cancer patients in the definitive or neoadjuvant therapy setting (31).

Beyond concomitant chemotherapy, other retrospective studies found additional prognostic factors for OS after radiation treatment of elderly ESCC patients such as T and N stages, early tumor stage, treatment response, or nutritional status (13, 17, 29, 32, 33).

For definitive treatment, radiotherapy was prematurely discontinued in 10% of patients, and the full treatment regimen of definitive chemoradiotherapy including all concomitant and adjuvant chemotherapy cycles could only be administered to 41% of patients due to treatment-related toxicities. Definitive radiotherapy alone was performed in 19% of the patients because they were classified as unfit for concurrent chemotherapy. Compared with the RTOG 8501, ARTDECO, or PRODIGE5/ACCORD17 trials, treatment compliance was substantially worse in our older patient population, although severe and life-threatening adverse events were documented less frequently (5, 20, 34, 35). As an explanation for this discrepancy, treatment de-escalation in older patients is more readily performed in case of mild-to-moderate acute side effects than in younger patients.

In the neoadjuvant setting, treatment adherence was substantially better in our analysis with 71% of patients receiving the full treatment regimen of concomitant chemoradiation. Nevertheless, complete treatment delivery was still considerably worse in our elderly study population compared to the CROSS trial (6). Additionally, in our dataset, dose reduction of chemotherapy in the setting of concomitant chemoradiotherapy was relatively common. In this context, we demonstrated that definitive (chemo)radiotherapy, dose escalation with brachytherapy, and stent implantation were important baseline factors significantly associated with severe treatment-related acute toxicities.

Albeit our analysis provides comprehensive data on treatment adherence, toxicity and outcome in one of the largest multi-center cohorts of elderly ESCC patients undergoing neoadjuvant or definitive chemoradiation, it has limitations due to its retrospective character. For example, detailed information on concomitant diseases and data on clinical factors such as patients' nutritional status, laboratory parameters (e.g., CRP levels or renal function at baseline and during treatment), or smoking status could not be systematically collected. Furthermore, patients' quality of life could not be assessed retrospectively and requires further prospective investigation. Retrospective evaluation of the general condition may have a high interobserver variability, thus geriatric assessments including many different domains of life of elderly patients such as functional, nutritional, cognitive, psychosocial and socioeconomic status may provide a more reliable assessment of patient performance (36). The ability of geriatric assessments to predict chemotherapy-associated toxicities has been shown in other cancers, so the relevance of geriatric assessments should be further addressed in future prospective studies (37, 38).

Conclusion

In summary, our multi-center analysis of 161 elderly ESCC patients indicates that chemoradiotherapy results in respectable LRC but relatively low OS and, in a substantial proportion of elderly patients, treatment-related acute toxicities which required dose reduction of radiotherapy and/or chemotherapy in the setting of neoadjuvant or definitive (chemo)radiotherapy. We demonstrated that concomitant chemoradiation without dose reduction of chemotherapy is the key prognostic factor for improved PFS, DMFS and OS of elderly patients with SCC of the esophagus. Therefore, it is of strong importance to carefully select those patients suitable for standard treatment, and further analyses are required to identify predictive factors for the tolerability of concurrent systemic treatment in elderly patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committees of the medical faculties of the universities of Mainz (no reference number), Freiburg (reference no. 275/18) and Heidelberg (reference no. S-040/2018). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TB, SA, DW, and NN developed and planned the analysis. DW is responsible for statistical considerations/basis of the analysis. TB, SA, AM, EN, DW, MMu, SK, AR, A-LG, JD, CF, MMö, PG, HS, and NN participated in data collection and/or interpretation of the results. TB and NN wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1063670/full#supplementary-material

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EDITED BY
Chi Lin,
University of Nebraska Medical Center,
United States

REVIEWED BY
Leilei Wu,
Tongji University, China
Muhammad Ali Shahiman,
Rawalpindi Medical University, Pakistan

*CORRESPONDENCE
Yajuan Lv
xiaochong9696@163.com

†These authors have contributed equally to this work

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Effect of intensity modulated radiotherapy on lymphocytes in patients with esophageal squamous cell carcinoma and its clinical significance

Xiufang Tian[1†], Yong Hou[1†], Jianping Guo[2], Haiyan Wu[3], Limin Nie[4], Hang Wang[5], Yan Zhang[6] and Yajuan Lv[1*]

[1]Department of Oncology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Key Laboratory of Rheumatic Disease and Translational Medicine, Shandong Lung Cancer Institute, Jinan, Shandong, China, [2]Department of Oncology, Maternal and Child Health Care Hospital of Zibo, Zibo, Shandong, China, [3]Department of Pharmacy, Central Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, [4]Department of Pathology, Caoxian People's Hospital, Shandong, Heze, China, [5]Department of Graduate, Shandong First Medical University, Jinan, Shandong, China, [6]Department of Clinical Medicine, Shandong University, Jinan, Shandong, China

Background: Radiotherapy usually leads to a decrease in the total number of lymphocytes in patients with esophageal cancer. The factors that causing lymphopenia and the clinical significance of lymphopenia are studied in this article.

Patients and methods: 110 patients with esophageal squamous cell carcinoma who had undergo intensity-modulated radiation therapy were enrolled. Statistical methods were used to analyze the correlation between lymphopenia and total survival in patients with esophageal cancer during radiotherapy, and analyze the correlations between nutritional factors and lymphopenia.

Results: There were 11 patients with the lowest lymphocyte value with level 1-2 during radiotherapy, accounting for 10% of all the patients, and 110 patients with level 3-4, accounting for 90% of all the patient. In all the enrolled patients, the incidence of lymphocyte nadir G1, G2, G3 and G4 MinALC during radiotherapy accounted for 0.91%, 9.09%, 62.73% and 27.27%, respectively.KM survival analysis showed that the overall survival of patients in the group (MinALC $\leq 0.41\times10^9$/L) was significantly lower than that of the patients in the other group (MinALC>0.43×10^9/L). Nutritional indicators were positively correlated with the decline degree of lymphocytes. The minimal value of lymphocyte can predict the occurrence of grade 3-4 radiation pneumonitis.

Conclusion: Lymphopenia induced by radiotherapy can predict survival and radiation pneumonitis. Nutritional factors such as hemoglobin and albumin were positively correlated with total lymphocytes numbers induced by radiotherapy.

KEYWORDS

esophageal squamous cell carcinoma, lymphopenia, nutritional factors, survival, radiotherapy

1 Introduction

Esophageal cancer is a malignancy that has a poor prognosis, which is mainly due to patients presenting once the cancer is in the advances stages. Esophageal cancer(EC) is a serious malignancy with a poor prognosis (1). It has been reported 5-year survival rate of about 20% in patients with esophageal cancer (2). In the world, EC is the eighth most common cancer, and the sixth deadliest (3, 4). There are two main reasons for the poor prognosis of esophageal cancer, one is diagnosis at advanced stages, and the other is that it is prone to distant metastasis (1). Concurrent chemoradiotherapy is the main treatment for locally advanced esophageal cancer. Human immune function plays an important role in tumor appearance, development, and prognosis. Radiotherapy can activate the immune system by generating an inflammatory response, inducing cytokine signaling cascades or promoting the release of tumor antigens or directly killing tumor cells to reduce tumor burden (5). In addition, the radiation dose and the duration of radiotherapy will damage the lymphocytes circulating in the radiation field to varying degrees, thereby inhibiting the immune function of the human body.

Treatment-related lymphopenia is closely associated with the prognosis of many malignancies, including esophageal cancer (6). In patients with esophageal cancer, it has been reported that lymphopenia during chemoradiotherapy is associated with worse progression-free survival (PFS) and overall survival (OS) (7).

The main purpose of this study was to investigate the changing trend of the total number of peripheral blood lymphocytes (ALC) in different periods of Intensity-Modulated Radiation therapy(IMRT) exposure and its clinical significance. We hypothesized that lymphocytes reduction is related to the overall survival of patients, and studied the correlation between the degree of lymphocyte reduction caused by radiotherapy and overall survival. This study also assumes that there is a correlation between the nutritional status and the degree of lymphocyte reduction. The most commonly used nutritional indicators such as albumin and hemoglobin were studied in this study.

2 Criteria for patient selection

All esophageal cancer patients enrolled in this study were from the radiotherapy department of our hospital. All esophageal cancer patients must meet the following criteria (1): Histopathologically diagnosed ESCC; (2) No surgery and no any anti-tumor therapy such as radiochemotherapy or immune, targeted therapy; (3) ECOG score of 0-2. (4) Age≥18 years old. (5) Before the start of radiotherapy, the liver function and renal function tests were less than 2 times of the upper limit of the normal range. The exclusion criteria are as follows: (1) a history of other primary malignancies other than esophageal cancer before radiotherapy;(2) serious medical diseases that may be life-threatening at any time, such as myocardial infarction, AIDS, uremia, etc. (3) Combined infectious diseases, rheumatism or blood system diseases. (4) Hypersplenism or splenectomy or liver resection or a history of organ transplantation. (5) Combined with distant organ metastasis. (6) Esophageal fistula or gastrointestinal bleeding occurred before treatment. (7) History of interstitial pneumonia or other pneumonia combined with abnormal pulmonary function.

All enrolled patients were clinically staged according to the American Joint Committee on Cancer/International Union Against Cancer(AJCC/UICC) esophageal cancer staging seventh edition. Between February 2013 and May 2020, a total of 110 patients with esophageal squamous cell carcinoma were enrolled. NCCN Guidelines (2022, version 1) recommended that radiotherapy and chemotherapy was the first choice for esophageal cancer patients with clinical stages of T1b-cT2,N+ or cT3-cT4b,N±. According to the clinical stage of AJCC(version 7), some patients in stage II,all patients in stage III and IVA are recommended to receive comprehensive treatment based on radiotherapy and chemotherapy. In our study,2 patients with stage I and 4 patients with stage IIA(cT2N0M0,G2-3) were enrolled. But these 6 patients refused surgery due to advanced age and other factors. According to the NCCN guidelines, patients with early stage esophageal cancer who refused surgery were recommended to radiotherapy. The remaining 104 patients with esophageal cancer were locally advanced stage, and radiotherapy ± chemotherapy were first recommended according to the NCCN guidelines. The radiotherapy indications of all the enrolled patients were reasonable. These patients were treated with intensity-modulated radiation therapy with or without concurrent chemotherapy in our hospital. The chemotherapy regimens for concurrent radiotherapy mainly include (1) platinum-based chemotherapy, cisplatin or nedaplatin (25mg/m^2 a day) with or without docetaxel (25mg/m^2 a day), once a week. (2) Oral fluorouracil chemotherapy drugs, capecitabine (850-1000mg/m^2, twice a day) or Sigio capsules (50-60 mg/m^2, twice a day) with concurrent radiotherapy orally every day.(3)Docetaxel (75mg/m^2, one day), with or without cisplatin 25mg/m^2 (days 1-3), once every 3 weeks.

3 General information and blood data collection and recording

The general information was collected through the hospital's electronic medical record system, such as age, gender and so on. The nutritional status of patients is expressed by serum albumin, prealbumin and hemoglobin. Within 2 weeks before radiotherapy, during radiotherapy, and within 1 month after radiotherapy, the peripheral blood data of all enrolled esophageal cancer patients were recorded, including the total number of peripheral blood lymphocytes, hemoglobin, and albumin values, etc. The time point before radiotherapy is represented by T1, the time point after radiotherapy is represented by T2, and the minimum value of ALC during radiotherapy is considered to be the lowest point of lymphocytes, which is represented by MinALC. According to the standardized Common Criteria for Adverse Events(CTCAE5.0), the range of grade 1 ALC reduction was: 0.8×10^9/L-lower limit of normal value, and the range of grade 2 ALC reduction was: 0.5-0.8×10^9/L, the range of grade 3 ALC reduction was 0.2-0.5×10^9/L, and the range of grade 4 ALC reduction was: 0-0.2×10^9/

L.Hypoalbuminemia was defined as serum albumin levels below 35 g/L.

4 Radiation therapy plan

All enrolled patients with esophageal cancer underwent treatment planning and dose distribution calculations using the Eclipse 10 planning system (Varian Medical Systems, Palo Alto, Calif). Large aperture CT (GE, discovery) was used for positioning, and head, neck and shoulder membranes or negative pressure pads were used for positioning and fixation. All patients were given IMRT. The radiotherapy prescription plan target volume (PTV) dose of the enrolled patients was 41.40-69.96 Gray(Gray, Gy)(once a day, 1.8-2.0 Gy each time, 5 times/week), and the median PTV prescription dose was 60Gy. All patients were irradiated with linear accelerator (truebeam,varian) X-rays. All radiotherapy plans are in accordance with the "National Comprehensive Cancer Network 2019 Guidelines for Esophageal Cancer", all radiotherapy plans involved organs at risk must meet the organ dose-volume constraints.

5 Statistical analysis

All statistical analyses of data in this study were performed using SPSS 22.0 software (IBM SPSS, USA) and Medcalc software. Among them, parameters conforming to continuous normal distribution were expressed as mean ± standard deviation (SD) or median (minimum-maximum value). Independent samples t or chi-square tests were used to analyze the differences between continuous and categorical variables between groups. Paired samples t-test was used to compare the same parameters at different time points. The predictive significance of parameters for overall survival was analyzed by univariate COX regression analysis, where univariate COX analysis (P<0.1) was used to construct a multivariate risk survival model for COX multivariate analysis (forward: wald method). Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of blood parameters in predicting overall survival (OS) with death status as the endpoint, and to determine cutoff points. The possible related factors of lymphocyte reduction were analyzed by ROC curve. Kaplan-Meier survival analysis was used to analyse the significance of individual parameters for predicting OS. Pearson analysis and scatter plot were used to analyze the correlation between nutritional parameters and MinALC/T1ALC ratio. All P values in this study were two-sided, and statistical significance was defined as P< 0.05.

6 Result

6.1 General characteristics of patients

Finally, a total of 110 patients with esophageal cancer in this study met the inclusion criteria and were included in this study. The general characteristics of patients with esophageal cancer were showed in Table 1. A total of 26 women and 84 men were enrolled in this study, and the median age at diagnosis of esophageal cancer was 67.5 years(range 36-79 years). Among them, there were 48 patients with cervical and upper thoracic esophageal cancer, 43 with middle thoracic esophageal cancer, and 19 with lower thoracic esophageal cancer. Among them, there were 2 patients with clinical stage I, 42 patients with stage II, 46 patients with stage III, and 20 patients with stage IV. There were 57 patients who received concurrent chemoradiotherapy and 53 patients who received only radiotherapy. A total of 24 patients had lymphopenia before radiotherapy, accounting for 21.82% of the total patients.The median prescribed dose of PTV was 6000cGy, ranging from (4140-6996)cGy. There were 11 patients with the lowest lymphocyte value with level 1-2 during radiotherapy, accounting for 10% of all the patients, and 110 patients with level 3-4, accounting for 90% of all the patients (Table 1). In all enrolled patients, the incidence of lymphocyte nadir G1, G2, G3 and G4

TABLE 1 Characteristics of patients with esophagus cancer.

Characteristic	Median (range)	Numbers of patients
Age (years)	67.5 (36-79)	
≤60		25
>60		85
Sex		
Male		84
Female		26
Tumor location		
Cervical or Upper thoracic		48
Middle thoracic		43
Lower thoracic		19
AJCC clinical stage		5
I		2
II		42
III		46
IVA		20
Radiation dose(cGy)	6000 (4140-6996)	
Concurrent chemotherapy		
No		53
Yes		57
Pre RT lymphopenia		
Yes		24
No		86
MinALC during RT		
Grade1-2		11
Grade3-4		99

MinALC during radiotherapy accounted for 0.91%, 9.09%, 62.73% and 27.27%, respectively.

6.2 Comparison of peripheral blood parameters in single radiotherapy and concurrent chemoradiotherapy groups

The number of white blood cells in the single radiotherapy group was slightly higher than that in the concurrent chemoradiotherapy group before RT(P=0.049, Table 2). During radiotherapy, there was no significant difference in the nadir value of lymphocytes between the two groups, and the white blood cells in the concurrent chemoradiotherapy group were significantly lower than those in the single radiotherapy group (P=0.012, Table 2). There was no significant difference in the total number of white blood cells and lymphocytes between the two groups in 1 month after radiotherapy (Table 2).

6.3 Dynamic changes of peripheral blood parameters at different time points of radiotherapy

White blood cells, total lymphocytes, hemoglobin and albumin, and serum prealbumin were significantly decreased during radiotherapy compared with those before radiotherapy (Table 3, P<0.001). All peripheral blood parameters after RT were still significantly lower than those before RT other than albumin and prealbumin. (P<0.001, Table 3).

6.4 KM survival analysis of lymphocyte count and overall survival

Lymphopenia before RT was defined as ALC<1.1×10^9/L. Before radiotherapy, whether the peripheral blood lymphocyte count was less than 1.1×10^9/L was divided into two groups. There was no significant difference between the two groups in KM survival analysis (Figure 1A, P=0.59). According to the end point of death or not, ROC curve analysis found the cut-off value of the lowest lymphocyte value during radiotherapy (MinALC ≤ 0.41×10^9/L) and divided all patients into two groups. KM survival analysis was used to compare the survival difference between these two groups. The overall survival of patients in the group (MinALC ≤ 0.41×10^9/L) was significantly lower than that of the patients in the other group (MinALC>0.43×109/L, Figure 1B, P=0.04).

TABLE 2 Comparison of WBC and ALC in patients with or without concurrent chemotherapy at different time points.

Parameters	Single RT	CRT	t	P
WBC(T1)	7.25 ± 3.03	6.28 ± 1.90	1.994	0.049
ALC(T1)	1.59 ± 0.54	1.60 ± 0.76	-0.135	0.893
Min WBC	3.43 ± 1.04	2.96 ± 0.92	2.555	0.012
Min ALC	0.32 ± 0.16	0.28 ± 0.14	1.43	0.155
WBC(T2)	5.17 ± 3.17	4.88 ± 2.96	0.499	0.618
ALC(T2)	0.46 ± 0.28	0.47 ± 0.33	-0.224	0.824

6.5 Univariate, multivariate COX overall survival analysis

Univariate COX analysis was performed on each parameter that might be predict survival, and then a multivariate COX proportional hazards survival model was constructed. Univariate COX test showed that the parameter that may predict the overall survival were clinical stage, MinALC(≤0.41 vs >0.41) (Table 4, P<0.05). Univariate COX analysis (P<0.1) entered into COX multivariate analysis (forward:wald). In addition to the above 2 factors, MinPA (<200 vs. ≥200mg/L) also entered in multivariate regression analysis. Finally, COX multivariate analysis showed that MinALC may predict the overall survival (see Table 4, P<0.05).

6.6 Correlation between the ratio of minimal ALC to ALC before RT and nutritional factors

In order to find whether there is a correlation between the degree of lymphocyte reduction during radiotherapy and nutritional factors, we take MinHb/T1Hb, MinAlb/T1Alb, MinPA/T1PA as the X-axis, and MinALC/T1ALC as the Y-axis.Pearson correlation bivariate statistical analysis was used. The results were shown in Figure 2, MinHb/T1Hb as the X-axis, P=0.015,MinAlb/T1Alb as the X-axis,P=0.049,MinPA/t1PA as the X-axis,P=0.021.These three nutritional indicators were positively correlated with the decline degree of lymphocytes.

6.7 ROC curve predicts the occurrence of grade 3-4 radiation esophagitis and radiation pneumonitis

As shown in Figure 3, taking the occurrence of grade 3-4 radiation esophagitis and radiation pneumonitis as the end points, and the MinALC during radiotherapy as a variable, which is calculated by ROC curve analysis. The results showed that MinALC predicted the occurrence of grade 3-4 radiation pneumonitis (AUC=0.676,P=0.0007, Figure 3A). However, the prediction of the occurrence of grade 3-4 radiation esophagitis was poor (AUC=0.573,P=0.272, Figure 3B).

6.8 Pearson correlation of MinALC/T1ALC and radiation dose factors

In order to study the correlation between dose and units which related to the degree of lymphopenia, we collected and recorded dosimetric parameters through DVHs. We take MinALC/T1ALC as

TABLE 3 Dynamic change of parameters in esophageal patients over time.

Parameters	T1	Min value during RT	T2	Total P	P1	P2	P3
WBC	6.75 ± 2.55	3.19 ± 1.01	5.02 ± 3.05	<0.001	<0.001	<0.001	<0.001
ALC	1.60 ± 0.66	0.30 ± 0.15	0.47 ± 0.30	<0.001	<0.001	<0.001	<0.001
Hemoglobin	129.99 ± 17.46	113.12 ± 14.74	16.04 ± 17.89	<0.001	<0.001	0.037	<0.001
Albumin	40.29 ± 5.03	36.57 ± 4.80	36.79 ± 5.62	<0.001	<0.001	0.587	<0.001
Prealbumin	208.94 ± 58.36	179.79 ± 61.54	180.38 ± 61.15	<0.001	<0.001	0.908	<0.001

Total P, comparison between the three groups; P1, comparison between T1 and Min value during RT; P2, comparison between T1 and T2; P3, comparison between Min value during RT and T2.

the Y-axis, and physical factors such as the average dose of PTV, Mus as X-axis, and Pearson bivariate analysis was used to analysis. The degree of MinALC/T1ALC reduction is significantly negatively correlated with the following dose factors(heart max dose, heart mean dose and lung mean dose)(P<0.05, Table 5).

7 Discussion

7.1 The relationship between lymphopenia induced by radiotherapy and prognosis

Esophageal cancer has the characteristics of high incidence and high mortality, and has an extremely poor prognosis, with a median 5-year survival rate of about 15%-25% (8). Peripheral blood lymphocytes are one of the important members of the human immune system and can reflect the immune function of the human body. Radiation therapy induces lymphopenia, which is associated with a radiation-induced immunosuppressive effect and is common in patients with malignancies (9, 10). One study had reported that grade 4 lymphopenia during chemoradiation was occurred in approximately 31 percent of all the patients (9). Studies have shown that about 37% of patients have grade 4 lymphopenia during CRT, and patients with grade 3-4 lymphopenia are more likely, about 91% (10). This study also reported that patients with grade 4 lymphopenia during CRT had significantly shorter PFS and OS than those without grade 4 lymphopenia (PFS: median 19.1 months vs. 61.7 months and OS: median 34.7 and 63.1 months, respectively) (10). A study had reported that radiotherapy combined with or without chemotherapy can induce severe lymphopenia, which is closely related to the prognosis of patients with various malignant tumors (7). The authors of Davuluri et al. found that the probability of grade 1, 2, 3, and 4 lymphopenia during CRT for esophageal cancer was 2%, 12%, 59%, and 27%, respectively. However, only grade 4 lymphopenia was associated with worse OS (7). An article found that patients with grade 4 lymphopenia had a poorer clinical prognosis, including OS, PFS, and distant metastasis-free survival than patients without grade 4 lymphopenia (11). A study of radiotherapy for esophageal cancer showed that the tumor progression rate and cancer-related mortality were significantly higher in the post-treatment lymphopenia group than in the post-treatment ALC count≥200 cells mm^3 group (76.4% vs. 52.8%, P<0.001; 58.4% vs. 39.6%, P=0.003) (9). The mechanisms underlying the association of lymphopenia with poorer survival in malignancies are not fully understood. Animal experiments have found that radiation can promote the release of antigens to stimulate lymphocytes, which can activate lymphocyte-mediated anti-tumor immune responses, resulting in anti-tumor effects (12). Some authors have found that tumor-infiltrating lymphocytes increase in patients after radiotherapy and chemotherapy, which can recognize non-natural antigens and then lead to tumor cell death (13). The correlation

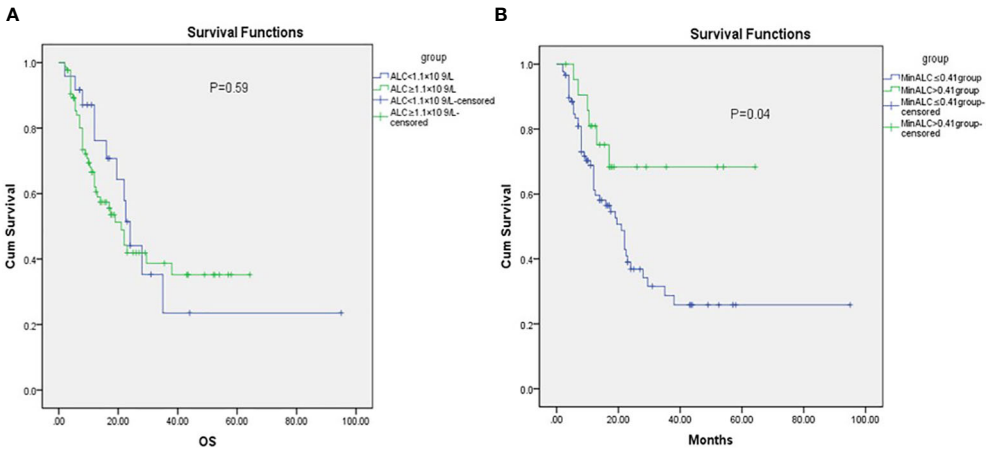

FIGURE 1
KM analysis of OS before RT [**(A)** ALC<1.1×10^9/L VS ALC≥1.1×10^9/L,P=0.59, **(B)** MinALC>0.41×10^9/L VS MinALC≤0.41×10^9/L,P=0.04].

TABLE 4 Univariate and multivariate COX analysis of overall survival for all patients.

Parameters	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (≤60 vs>60)	1.209	0.743-1.967	0.445			
Sex (male vs female)	1.069	0.658-1.736	0.787			
Stage (I-II vs III-IV)	1.359	1.009-1.829	0.043			
T1WBC (>8.24 vs ≤8.24)	0.503	0.756-1.771	0.503			
T1ALC (≤1.1vs>1.1)	0.94	0.586-1.507	0.796			
MinALC (≤0.41 vs >0.41)	0.032	0.004-0.264	0.001	0.032	0.004-0.264	0.001
CRT vs single RT	0.744	0.484-1.144	0.178			
MinAlb (<35 vs ≥35g/L)	0.748	0.483-1.161	0.748			
MinPA (<200vs ≥200mg/L)	0.662	0.426-1.030	0.067			

between lymphocyte reduction and prognosis may be related to the inhibition of immune function by radiotherapy. First, radiotherapy rays that cause suppression of bone marrow activity which leading to a decrease in the number of lymphocytes generated. And rays can also damage lymphoid organs such as the thymus or spleen, which may lead to immunosuppression (14). In addition, radiotherapy rays can directly damage the normal function of peripheral blood lymphocytes and directly inhibit immune function (9). Our study found that there was no significant difference in the nadir value of lymphocytes in patients with or without combined chemotherapy during radiotherapy (Table 2). In addition, WBC, hemoglobin, albumin, and serum prealbumin were significantly decreased during radiotherapy compared with those before radiotherapy (Table 3, P<0.001). After radiotherapy, all parameters recovered, but ALC recovered more slowly (Table 3). The OS of patients in the MinALC ≤ 0.41×10^9/L group was significantly lower than that of the patients in the MinALC>0.41×10^9/L group (Figure 2B, P=0.04). In addition, COX multivariate analysis showed that MinALC(≤0.41 vs.>0.41×10^9/L) was significantly associated with OS (Table 4, P=0.001).

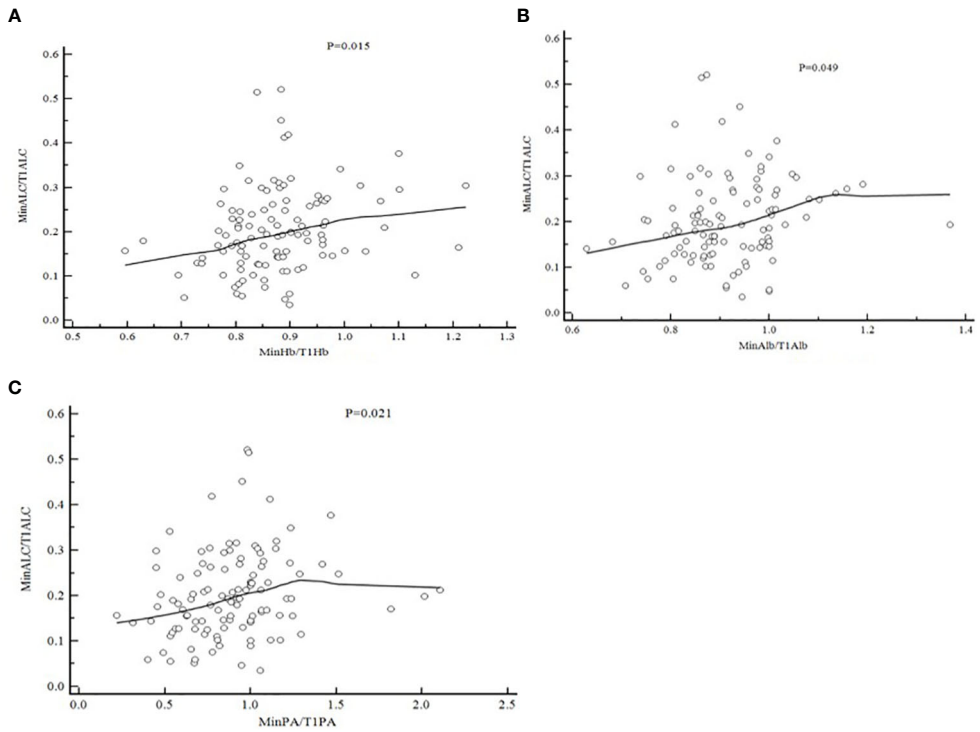

FIGURE 2
Pearson Correlation of MinALC/T1ALC and nutritional factors [**(A)** MinHb/T1Hb and MinALC/T1ALC,P=0.015; **(B)** MinA1b/T1A1b and MinALC/T1ALC, P=0.049; **(C)** MinPA/T1PA and MinALC/T1ALC,P=0.021].

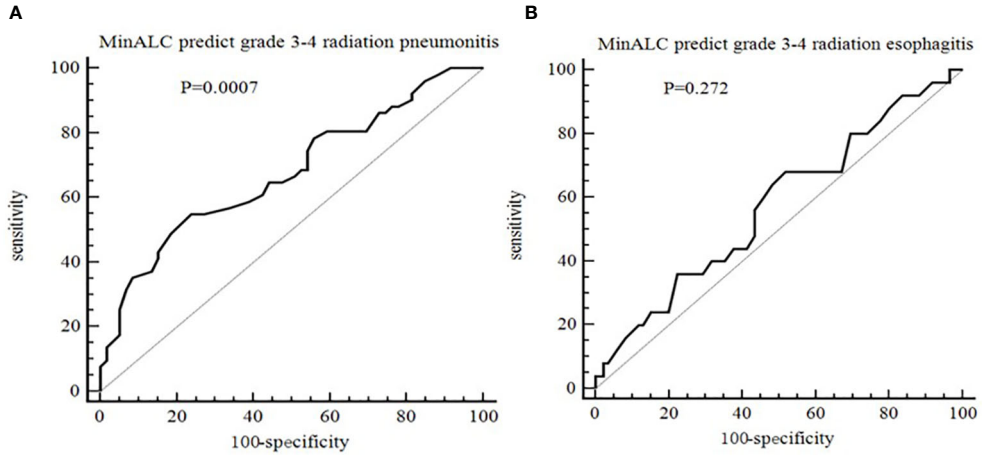

FIGURE 3
ROC curve for the prediction of radiation side effect [**(A)** MinALC predict grade 3-4 radiation pneumonitis, AUC=0.676,P=0.0007; **(B)** MinALC predict grade 3-4 radiation esophagitis, AUC=0.573,P=0.272].

7.2 The relationship between nutritional factors and lymphocytes

In addition to immunity status, the nutritional status of individuals is closely related to the prognosis of various malignancies (15, 16). The most typical clinical symptom of esophageal cancer patients is a progressive feeling of blocking eating. Because of direct involvement in eating, the probability of malnutrition in patients with esophageal cancer ranks first among all malignant tumors (17). Low albumin is a common malnutrition expression in patients with malignant tumors, which is a typical manifestation of cachexia and is related to the prognosis of patients with various malignant tumors, including esophageal cancer (18, 19). Many studies have shown that albumin can prevent tumorigenesis by stabilizing cell growth and inhibiting DNA replication (20). Basic experiments show that the activation of T and B lymphocytes *in vitro* requires the presence of serum albumin (21). High-protein dietary intervention in cancer patients may stimulate the body's immune response.A study had showed that a low-carbohydrate, high-protein combination diet (10.6% carbohydrate, 63.5% protein) slows down the rate of tumor growth in mice compared to a traditional diet (55.2% carbohydrate, 23.2% protein) (22). And mice with a high-protein diet had less chromosomal damage in the bone marrow and reduced oxidative damage in the liver and spleen compared with mice with a low-protein diet (23). A study found that a lower level of albumin was an independent predictor of early death (less than 6 months) in esophageal cancer (18). Lower albumin levels not only reflect poorer nutritional status, but also reflect tumor aggressiveness status (18). Low hemoglobin, or anemia, is the main determinant of whether human tumor cells are hypoxic and can directly affect the sensitivity of tumor cells to radiotherapy (24). Studies have shown that malnutrition such as anemia causes many adverse clinical consequences, including reduced sensitivity to treatments such as RT, increased risk of treatment toxicity during anti-tumor periods, and reduced survival (25). At present, whether there is a correlation between the changes of hemoglobin and albumin and the decrease of lymphocytes during radiotherapy for esophageal cancer has not been reported. Patients with cachexia usually experience lymphopenia due to decreased production of cell-stimulating factors (26). Our study showed that MinHb/T1Hb,MinAlb/T1Alb,MinPA/t1PA were significantly positively correlated with the ratio of MinALC/T1ALC (Figure 2, P<0.05). Our study showed that the nutritional status of patients is closely related to the degree of lymphopenia, so it is important to strengthen nutritional support for patients with esophageal cancer during radiotherapy.

7.3 The relationship between lymphopenia induced by radiotherapy and radiation pneumonitis

Zhou et al. showed that the decrease in lymphocyte count in lung cancer patients reflected the severity of radiation pneumonitis. Values of lymphocytes and CD4+ T lymphocyte subsets proved as independent predictors of radiation pneumonitis. The lower peripheral blood levels of lymphocytes and CD4+ T lymphocyte were associated with an increased risk of radiation pneumonitis,

TABLE 5 Pearson correlation of MinALC/T1ALC and radiation dose factors.

Parameters	MinALC/T1TLC		
	r	95%CI	P
PTV max dose	-0.046	-0.232–0.141	0.626
PTV mean dose	-0.032	-0.218–0.156	0.741
Heart max dose	-0.209	-0.381–-0.023	0.028
Heart mean dose	-0.268	-0.433–0.085	0.005
Lung max dose	-0.071	-0.255–0.118	0.459
Lung mean dose	-0.348	-0.502–-0.172	<0.001
Machine Units	-0.129	-0.309–0.059	0.177

which was validated by this mice model (27). Yang et al. showed that the platelet-to-lymphocyte ratio during treatment (P=0.027), and neutrophil-to-lymphocyte ratio at the end of treatment (P=0.001) were the independent predictors for symptomatic radiation pneumonitis in patients with Esophageal Cancer (28). Zhang et al. revealed that Higher CD8+ T cell count after radiotherapy in lung cancer patients was associated with an increased risk of radiation pneumonitis (29). The neutrophil-lymphocyte ratio(NLR) was higher in patients who developed symptomatic radiation pneumonitis (p=0.012).The NLR is a useful biomarker for predicting symptomatic radiation pneumonitis development after RT in NSCLC patients (30). And a study showed that lymphocyte percentage was related to radiation pneumonia in patients with lung cancer after RT(P<0.05) (31). Recent a study showed that Pre- and post-RT percentage of CD8+ T cell were the independent factors of ≥grade 2 radiation pneumonia in patients with esophageal squamous cell carcinoma (32). In our study, we found that MinALC could predict the occurrence of grade 3-4 radiation pneumonitis (P=0.0007, Figure 3A). This result may be related to the decrease of lymphocytes that caused by radiation rays, which leads to a decline in immune function and is more likely to cause pneumonia. Due to the limited sample size, this result still needs to be confirmed by a large sample of clinical trials. Severe pneumonia can directly lead to the death of patients. Therefore, for patients with poor lung function before radiotherapy, the irradiated volume and dose of bilateral lungs should be strictly controlled.

This study has its own limitations. Firstly, this study is a retrospective study, maybe there are many selective biases when selecting patients (for example, more elderly patients were enrolled, because elderly patients are more inclined to refuse surgery). Secondly, due to the small number of patients enrolled, the subgroup analysis is not conducted for different groups of chemotherapy schemes and chemotherapy doses. Thirdly, due to the limitation of the retrospective study, the factors that may cause lymphopenia cannot be fully included, such as whether the patient uses other drugs that may cause lymphopenia during radiotherapy. Therefore, all the findings of this article still need to be further confirmed by large-scale prospective research.

8 Conclusion

Although there were many limitations in this article, the results still showed that lymphopenia can be used to predict survival and radiation pneumonitis. The decline of total lymphocytes values during radiotherapy could predict the survival time of esophageal cancer. Nutritional factors such as hemoglobin and albumin were positively correlated with total lymphocytes values induced by radiotherapy. During radiotherapy, strengthening nutritional support may reduce the degrees of lymphopenia caused by radiotherapy and may prolong the survival time.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Shandong Qianfoshan Hospital (Number:S008). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

(I) Conception and design: YL. (II) Collection and assembly of data: YH, XT, LN. (III) Data analysis and interpretation: JG, HWu, YZ, HWa. (IV) Manuscript writing: All authors. (V) All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Alberto Puccini,
Ospedale Policlinico San Martino IRCCS, Italy

REVIEWED BY
Stefano Bona,
Humanitas Research Hospital, Italy
Ugo Elmore,
San Raffaele Hospital (IRCCS), Italy
Beatriz Martin-Perez,
University Hospital of Badajoz, Spain

*CORRESPONDENCE
Xishan Wang
wxshan1208@126.com

†These authors have contributed equally to this work and share first authorship

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Development of artificial blood loss and duration of excision score to evaluate surgical difficulty of total laparoscopic anterior resection in rectal cancer

Jingfang Lv†, Xu Guan†, Ran Wei, Yefeng Yin, Enrui Liu, Zhixun Zhao, Haipeng Chen, Zheng Liu, Zheng Jiang and Xishan Wang*

Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Purpose: Total laparoscopic anterior resection (tLAR) has been gradually applied in the treatment of rectal cancer (RC). This study aims to develop a scoring system to predict the surgical difficulty of tLAR.

Methods: RC patients treated with tLAR were collected. The blood loss and duration of excision (BLADE) scoring system was built to assess the surgical difficulty by using restricted cubic spline regression. Multivariate logistic regression was used to evaluate the effect of the BLADE score on postoperative complications. The random forest (RF) algorithm was used to establish a preoperative predictive model for the BLADE score.

Results: A total of 1,994 RC patients were randomly selected for the training set and the test set, and 325 RC patients were identified as the external validation set. The BLADE score, which was built based on the thresholds of blood loss (60 ml) and duration of surgical excision (165 min), was the most important risk factor for postoperative complications. The areas under the curve of the predictive RF model were 0.786 in the training set, 0.640 in the test set, and 0.665 in the external validation set.

Conclusion: This preoperative predictive model for the BLADE score presents clinical feasibility and reliability in identifying the candidates to receive tLAR and in making surgical plans for RC patients.

KEYWORDS

rectal cancer, totally laparoscopic anterior resection, surgical difficulty, BLADE score system, random forest algorithm

Introduction

The fast development of laparoscopic surgery indicated great progress in the treatment of colorectal disease in past decades. Substantial evidence suggests that laparoscopic anterior resection (LAR) benefits rectal cancer (RC) patients through a high-definition surgical field, bleeding reduction, early recovery of bowel function, and short hospital stay (1–3). However, conventional LAR requires an abdominal incision for specimen extraction and digestive reconstruction. Despite the incision of LAR being smaller than it is in open surgery, it still causes incisional infection, postoperative pain, and incisional hernia, which could reduce the advantages of minimally invasive laparoscopic surgery (4–6). The introduction of total LAR (tLAR) with intracorporeal anastomosis and natural orifice specimen extraction (NOSE) has led to improvement of short-term outcomes caused by incision (7–9) and has comparable 3-year disease-free and overall survival with those in conventional laparoscopy (10), which has therefore inspired further exploration and popularization of tLAR in the treatment of RC (11–15). However, tLAR is challenged by complicated surgical procedures and high surgical difficulty of intracorporeal anastomosis, as well as potential concerns regarding intraperitoneal contamination and dissemination of tumor cells (11, 16–19).

Scoring systems of surgical difficulty not only help to identify patients with a high risk of postoperative complication and poor prognosis but also help surgeons to select appropriate cases and make surgical plans. Although the predictors of the difficulty of anterior resection have been identified (20–22), no scoring systems have been developed for tLAR. Here, we performed this study with the aims of a) developing a simple clinical tool named blood loss and duration of excision (BLADE) scoring system to evaluate the surgical difficulty of tLAR, b) assessing the effect of the BLADE score on short-term outcomes for RC patients undergoing tLAR, and c) using preoperative variables to establish the predictive model for the BLADE score based on machine learning algorithms.

Materials and methods

Study population

A total of 3,485 RC patients treated with tLAR between August 2008 and July 2021 were collected from the China national database of tLAR and NOSE for colorectal cancer. The data were collected by a secure online platform (http://chinanoses.yiducloud.com.cn) and stored in a uniform format. This study was reviewed and approved by the institutional review board of China National Cancer Center and was exempt from patient consent given the retrospective nature of the study. All included patients were pathologically diagnosed with adenocarcinoma located within 15 cm from the anal verge. The exclusion criteria for tLAR were as follows: patient with multiple lesions, tumor spreading to other distant organs or invading adjacent organs, the patient underwent conversion to conventional laparoscopic surgery or open surgery, surgery performed with a robotic platform, and patient with incomplete data. The flowchart is presented in Figure 1.

Variable selection

The clinical records of RC patients were extracted with the following information for analysis: patient characteristics [gender, age at diagnosis, body mass index (BMI), and comorbidity], tumor characteristics [distance from lower edge of tumor to anus, tumor size, American Joint Committee on Cancer (AJCC) TNM stage, preoperative serum carcinoembryonic antigen (CEA), preoperative serum carbohydrate antigen 19-9 (CA19-9), and receipt of neoadjuvant chemoradiotherapy], surgical information (estimated blood loss and surgical time), and 30-day postoperative complications (anastomotic leakage, anastomotic bleeding, anastomotic stenosis, intraabdominal bleeding, intraabdominal abscess, rectovaginal fistula, intestinal obstruction, wound complications, pulmonary disease, urinary disease, and others).

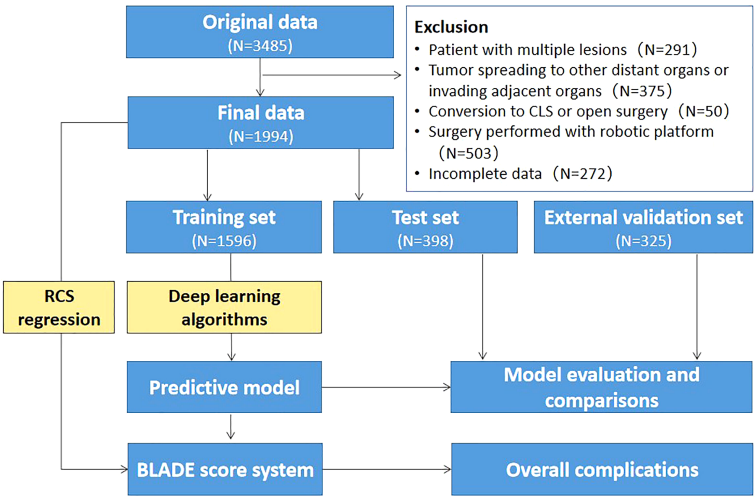

FIGURE 1
Flowchart illustrating patient selection and the overall data analysis procedures. RCS, restricted cubic spline; BLADE, blood loss and duration of excision; LR, logistic regression; CLS, conventional laparoscopic surgery.

Surgical procedures of tLAR

All surgical procedures of tLAR were performed by experienced colorectal surgeons for laparoscopic surgery. The tLAR was performed as described previously (23). Briefly, the main surgical procedures of tLAR were as follows: a) anterior resection was performed following the principle total mesorectal excision (TME), b) digestive tract reconstruction included low colorectal end-to-end anastomosis or coloanal end-to-end anastomosis, and c) the rectal specimen was finally extracted transanally or transvaginally. In brief, all procedures of anterior resection and digestive tract reconstruction were performed intraabdominally.

Development of BLADE scoring system

The surgical difficulty grading of the BLADE scoring system was built by two surgical variables including duration of surgery and estimated blood loss. Operative time was defined as the time from skin incision to final cutaneous closure. Anesthesiologists carefully evaluated blood loss during the operation and recorded it at the end of the operation. Restricted cubic spline (RCS) regression plots were performed to examine the full-range associations between the duration of surgery and the estimated blood loss with the odd ratios (ORs) for overall complication within 30 days to ascertain the optimal cutoff point to classify the operative time and total intraoperative blood loss into binary variables with a certain degree of objectivity. Each of the two intraoperative factors was assigned 1 point when it was at or above the threshold value. Therefore, the BLADE score ranged from 0 to 2, and patients scoring 0, 1, and 2 were classified as low, middle, and high difficulty of tLAR, respectively.

Establishment of the preoperative model to predict surgical difficulty

Of included patients from the national database, 80% (n = 1,596) were randomly selected for the training set, and the remaining 20% (n = 398) were used as the test set. Furthermore, 325 RC patients who underwent tLAR between January 2015 and August 2018 at Cancer Hospital Chinese Academy of Medical Sciences and the Second Affiliated Hospital of Harbin Medical University were identified as the external validation set according to the inclusion and exclusion criteria. The preoperative models for the BLADE score were developed based on the training cohort by using machine learning algorithms and then were tested in both the test set and the external validation cohort. Nine preoperative variables associated with surgical difficulty were obtained, including gender, age at diagnosis, BMI, history of previous diseases, receipt of neoadjuvant chemoradiotherapy, tumor location, tumor size, AJCC T stage, and AJCC N stage. The algorithms included logistic regression (LR), k-nearest neighbor (KNN), support vector machine (SVM), artificial neural network (ANN), generalized boosting machines (GBMs), and random forest (RF). The details of each model are described in Supplementary Table 1. We calculated the area under the receiver operating characteristic curve (AUC) as our primary performance metric to assess the discrimination of the machine learning algorithm.

Statistical analysis

The data were presented as the mean with standard deviation (SD) for continuous variables and proportions (%) for categorical variables. The association between surgical difficulty and overall postoperative complications was evaluated through uni- and multivariate binary logistic regression analyses by calculating ORs and 95% confidence intervals (CIs). The variables with a p-value of less than 0.05 after univariate analysis were included in the multivariate analysis. Statistically significant results were defined as $p < 0.05$, and all p-values were two-sided. Data analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp.) and R software version 3.5.3 (R Project for Statistical Computing). The study was reported in line with the STROCSS criteria (24).

Results

Patient characteristics and surgical outcomes

A total of 1,994 patients who underwent tLAR were identified, including 1,030 (51.7%) male and 964 (48.3%) female patients, with a median age of 60.20 (SD = 11.43) years and a mean BMI of 22.84 kg/m^2 (SD = 2.96). A total of 617 (30.9%) patients had comorbidities, and 101 patients (5.1%) had received neoadjuvant therapy. The mean duration of surgery was 188.59 (range 75–669) min, and the mean intraoperative blood loss was 75.85 (range 40–600) ml. The overall complication rate was 17.9% (356 of 1,994 cases). The details of patient information are shown in Table 1.

Development of BLADE scoring system

The effects of the duration of surgery and the estimated intraoperative blood loss on the ORs and 95% CI of overall complication were present using spline curve analysis. For the duration of surgery, the ORs continuously increased with an increase in the duration of surgery, and the slight plateau phase of the curve was detected between approximately 165 and 281 min (non-linearity p-values were 0.001) (Figure 2A). Increasing the duration of surgery at <165 and >281 min was associated with a rapid increase in the risk of overall complications after surgery. We then defined the duration of surgery performed ≥165 min as long duration (1 point) and the duration of surgery performed <165 min as short duration (0 point). The estimated intraoperative blood loss was associated with complications in a linear profile (non-linearity p-values were 0.911) (Figure 2B). Thus, we defined blood loss >60 ml (OR, 1.01; 95% CI, 0.996–1.015) as a large amount of bleeding (1 point) and ≤60 ml as a small amount of bleeding (0 point). Based on this new scoring system, 1,994 patients were scored retrospectively; 517 (25.9%), 989 (49.6%), and 488 patients (24.5%) were defined as low-, middle-, and high-difficulty groups, respectively (Table 2).

TABLE 1 Demographic and tumor characteristics of patients undergoing tLAR for RC.

Characteristics	Derivation set	Training set	Test set	External validation set
Gender, n (%)				
Male	1,030 (51.7)	835 (52.3)	195 (49.0)	203 (49.0)
Female	964 (48.3)	761 (47.7)	203 (51.0)	211 (51.0)
Age at diagnosis, mean (SD), years	60.20 (11.43)	60.08 (11.59)	60.67 (10.73)	61.54 (10.67)
Age at diagnosis, n (%), years				
<60	885 (44.4)	717 (44.9)	168 (42.2)	157 (37.9)
≥60	1,109 (55.6)	879 (55.1)	230 (57.8)	257 (62.1)
BMI, mean (SD), kg/m^2	22.84 (2.96)	22.836 (2.98)	22.87 (2.91)	22.49 (2.90)
BMI, n (%), kg/m^2				
<18.5	113 (5.7)	95 (6.0)	18 (4.5)	25 (6.0)
≥18.5, <25	1,437 (72.1)	1,144 (71.7)	293 (73.6)	308 (74.4)
≥25, <30	420 (21.1)	337 (21.1)	83 (20.9)	74 (17.9)
≥30	24 (1.2)	20 (1.3)	4 (1.0)	7 (1.7)
Comorbidity, n (%)				
No	1,377 (69.1)	1,107 (69.4)	270 (67.8)	86 (20.8)
Yes	617 (30.9)	489 (30.6)	128 (32.2)	328 (79.2)
Neoadjuvant chemoradiotherapy, n (%)				
No	1,893 (94.9)	1,517 (95.1)	376 (94.5)	403 (97.3)
Yes	101 (5.1)	79 (4.9)	22 (5.5)	11 (2.7)
Tumor location, n (%), cm				
<5	422 (21.2)	327 (20.5)	95 (23.9)	93 (28.6)
≥5, <10	695 (34.9)	570 (35.7)	125 (31.4)	144 (44.3)
≥10	877 (44.0)	699 (43.8)	178 (44.7)	88 (27.1)
Tumor size, mean (SD), cm	3.53 (1.39)	3.559 (1.42)	3.43 (1.24)	3.37 (1.14)
Tumor size, n (%), cm				
<5	1,681 (84.3)	1,339 (83.9)	342 (85.9)	360 (87.0)
≥5	313 (15.7)	257 (16.1)	56 (14.1)	54 (13.0)
T stage, n (%)				
T0–T2	737 (37.0)	573 (35.9)	164 (41.2)	348 (87.0)
T3–T4	1,257 (63.0)	1,023 (64.1)	234 (58.8)	66 (15.9)
N stage, n (%)				
N0	1,313 (65.8)	1,049 (65.7)	264 (66.3)	255 (61.6)
N1–2	681 (34.2)	547 (34.3)	134 (33.7)	159 (38.4)
CEA, n (%)				
Normal	1,327 (66.5)	1,056 (66.2)	271 (68.1)	228 (55.1)
Elevated	667 (33.5)	540 (33.8)	127 (31.9)	186 (44.9)
CA19-9, n(%)				
Normal	1,529 (76.7)	1,212 (75.9)	317 (79.6)	257 (62.1)
Elevated	465 (23.3)	384 (24.1)	81 (20.4)	157 (37.9)

(Continued)

TABLE 1 Continued

Characteristics	Derivation set	Training set	Test set	External validation set
Duration of surgery, mean (SD), min	188.59 (70.36)	188.48 (70.59)	189.06 (69.50)	157.32 (56.06)
Estimated intraoperative blood loss, mean (SD), ml	75.85 (47.37)	76.06 (48.04)	75.05 (44.61)	70.08 (51.31)
Postoperative complication, n (%)				
No	1,638 (82.1)	1,314 (82.3)	324 (81.4)	378 (91.3)
Yes	356 (17.9)	282 (17.7)	74 (18.6)	36 (8.7)

RC, rectal cancer; BMI, body mass index; SD, standard deviation; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; tLAR, total laparoscopic anterior resection.

Effect of BLADE score on postoperative complication

The multivariate logistic analysis was used to identify the association between the BLADE score and postoperative complication. In the derivation set, we found that male patients (OR, 1.438; 95% CI, 1.132–1.826, p = 0.003), patients with comorbidity (OR, 1.774; 95% CI, 1.390–2.265, p = 0.000), lower tumor location (OR, 2.183; 95% CI, 1.615–2.953, p = 0.000), and the BLADE scoring system (middle-difficulty, OR, 1.408; 95% CI, 1.013–1.955, p = 0.042; high-difficulty, OR, 2.423; 95% CI, 1.702–3.450, p = 0.000) were considered as the independent risk factors to postoperative complication for patients treated with tLAR. Similar findings of the association between the surgical difficulty of the BLADE score and complication were also presented in the external validation set (Table 3). The results above suggested that patients with higher difficulty levels were associated with a higher risk of complication after tLAR.

Establishment of the preoperative model to predict surgical difficulty

In order to identify the high-difficulty group, we combined patients in the low-difficulty group and patients in the middle-difficulty into one group. For logistic regression, we found that tumor location, comorbidity, and neoadjuvant therapy were considered predictors for the surgical difficulty of tLAR for RC patients (Supplementary Table 2). Moreover, we found that the AUC of the RF algorithm (0.786 in the training set; 0.640 in the test set; 0.665 in the external validation set, Figure 3) was significantly better than that of other models (Supplementary Table 1).

Discussion

Individualized treatment has been gradually emphasized in current clinical practice, and a useful and easy scoring system of surgical difficulty could help to identify patients with a high risk of having postoperative complications and patients with poor prognoses. Here, our study is the first report to develop an easy-to-use BLADE scoring system to evaluate the surgical difficulty for tLAR and validate the performance in an independent external cohort to evaluate the ability of true replication, which could reflect the generalizability of this scoring system in the clinical setting. Then, we used preoperative variables to establish the predictive model for the BLADE score based on machine learning algorithms.

The assessment of surgical difficulty is challenged by multiple factors that depend on the surgeon's experiences, the cooperation of the surgical team, and the surgical platform (25). Therefore, the variable selection in the grading system of surgical difficulty is sometimes debatable and subjective. Escal et al. recently developed

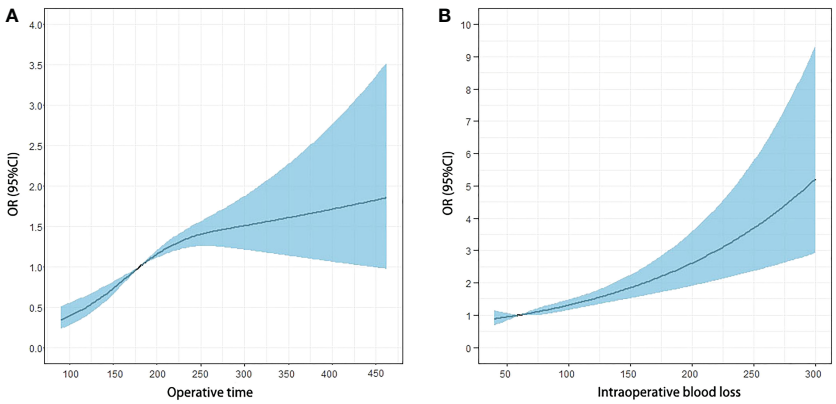

FIGURE 2
Odds ratio (OR) curves of the duration of surgery and the estimated blood loss for postoperative complication risk with spline curve analysis. **(A)** The OR continuously increased with the increase of the duration of surgery, and the plateau phase of the curve was detected around 165 and 281 min. The plateau phase continued until 281 min, and the OR increased again with the increase in the duration of surgery. **(B)** The estimated blood loss was associated with the OR of complication in a linear profile.

TABLE 2 Patient proportion of surgical difficulty for tLAR according to BLADE scoring system.

	Derivation set	Training set	Test set	External validation set
Operation time score, n (%)				
0	863 (43.3)	690 (43.2)	173 (43.5)	288 (69.6)
1	1,131 (56.7)	906 (56.8)	225 (56.5)	126 (30.4)
Operative blood loss score, n (%)				
0	1,158 (58.1)	928 (58.1)	230 (57.8)	233 (56.3)
1	836 (41.9)	668 (41.9)	168 (42.2)	181 (43.7)
BLADE score, n (%)				
0	517 (25.9)	406 (25.4)	111 (27.9)	166 (40.1)
1	989 (49.6)	807 (50.6)	182 (45.7)	189 (45.7)
2	488 (24.5)	383 (24.0)	105 (26.4)	59 (14.3)

tLAR, total laparoscopic anterior resection; BLADE, blood loss and duration of excision.

a grading system to evaluate the surgical difficulty of TME for locally advanced RC, including six intraoperative and postoperative variables, including conversion to laparotomy, blood loss, duration of surgery, use of transanal dissection (the transanal approach is required to complete TME in difficult surgical case), postoperative complications, and length of hospital stay. Then, a grading system was established based on these variables to classify the RC patients as at low-risk or high-risk of surgical difficulties (26). Based on this score grading system, Chen et al. (27), Yamamoto et al. (28), and de'Angelis et al. (29) made small modifications of variables to this system according to their own needs and then established the risk models to predict the surgical difficulty. The establishment of the above grading systems was based on intraoperative and postoperative variables, which indicated that both an unsuccessful resection and an extended postoperative course were related to surgical difficulty (26). However, we believe that the inclusion of postoperative variables into the scoring system should be cautiously considered for two reasons. First, the postoperative outcome, such as the length of hospital stay, is affected by a variety of uncontrollable factors, which makes it impossible to discern the association between the postoperative outcome and the surgical difficulty. Second, the above studies did not calculate the correlation between intraoperative variables and postoperative outcomes, leading to the inability to ensure that the variable selection met the statistical requirements of model establishment. Therefore, it is scientific and reasonable to establish a surgical difficulty evaluation system only based on intraoperative variables, which could objectively reflect the degree of difficulty in the surgical process. The score grading systems based on intraoperative variables have been established and validated in various types of surgery (30–36). In our study, we established a simple scoring system based on the intraoperative parameters of blood loss and duration of surgery, which was validated as having close associations with postoperative complications. In general, studies selected a median or alternative value as the cutoff value to divide patients into different groups, which weakens its clinical guiding significance. The results of the present study showed that although ORs continuously increased with an increase in the duration of surgery or blood loss, the RCS model (37) demonstrated a non-linear association between continuous operative time and outcome. Therefore, the optimal cutoff value should be 165 min, which maximizes the differences in ORs since the risk of postoperative complications increased at different rates before and after 165 min of surgical time. In contrast, the association between intraoperative blood loss and ORs of complications after surgery was linear. Blood loss <60 ml was the protective factor against complication, and when blood loss >60 ml, the ORs of complication were greater than 1. Therefore, we chose 60 ml as the optimal cutoff.

In addition, a previous study has established a surgical difficulty scoring system for TME surgery based on preoperative variables. Baek et al. have established a scoring system to assess the surgical difficulty of robotic surgery for RC according to MRI-based pelvimetry, including large tumor size, narrow intertuberous distance, shallow sacral angle, and long sacral length (38). Then, they categorized patients into three risk groups based on four risk factors: easy group (no risk factor), moderate group (one to two risk factors), and difficult group (three to four risk factors). There are many controversies in using preoperative variables to evaluate a surgical difficulty, but they should be considered as predictors of surgical difficulty to assist surgical decision-making. Several studies have identified many variables to predict the surgical difficulty of rectal resections. Gender, BMI, tumor location, tumor size, comorbidity, pelvic anatomical structure, neoadjuvant therapy, and surgeon experiences were identified as predictive factors for the duration of surgery, conversion to open surgery, and postoperative complications (26, 39–41). Similar to the results of previous studies, we found that tumor location, comorbidity, and neoadjuvant therapy were considered predictors for the surgical difficulty of tLAR for RC patients.

In light of recent developments in machine learning and the accessibility of computing power, the application of the technique in the data mining and model development field has yielded promising results (42). Currently, most of the predictive tools are presented with limited clinical applicability, poor predictive ability, and lack of external validation (28, 43, 44) since they are developed according to the variables' interaction in a linear and additive manner (45), but the surgical difficulty is multi-factorial, and the interaction between

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TABLE 3 Univariate and multivariate logistic regression analyses of postoperative complication.

	Derivation set				External validation set			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender								
Male	1.435 (1.137–1.810)	0.002	1.438 (1.132–1.826)	0.003	1.710 (0.849–3.444)	0.133		
Female	Ref.		Ref.		Ref.			
Age, years								
<60	Ref.				Ref.			
≥60	1.028 (0.816–1.295)	0.814			0.657 (0.331–1.307)	0.231		
BMI, kg/m^2								
<18.5	Ref.				Ref.			
≥18.5, <25	0.671 (0.426–1.056)	0.084			2.306 (0.300–17.717)	0.422		
≥25, <30	0.626 (0.378–1.036)	0.068			2.507 (0.293–21.452)	0.401		
≥30	2.275 (0.907–5.706)	0.080			4.000 (0.217–73.618)	0.351		
Comorbidity								
No	Ref.		Ref.		Ref.		Ref.	
Yes	1.880 (1.485–2.380)	0.000	1.774 (1.390–2.265)	0.000	0.284 (0.140–0.576)	0.000	0.487 (0.218–1.087)	0.079
Neoadjuvant therapy								
No	Ref.				Ref.			
Yes	0.860 (0.498–1.486)	0.588			1.051 (0.131–8.455)	0.962		
Tumor location, cm								
<5	2.590 (1.947–3.447)	0.000	2.183 (1.615–2.953)	0.000	2.225 (0.861–5.751)	0.099		
≥5, <10	1.263 (0.956–1.668)	0.100	1.178 (0.885–1.567)	0.261	0.864 (0.316–2.358)	0.775		
≥10	Ref.		Ref.		Ref.			
Tumor size, cm								
<5	Ref.				Ref.			
≥5	1.312 (0.973–1.768)	0.075			2.062 (0.887–4.796)	0.093		
T stage								
T0–T2	Ref.		Ref		Ref.		Ref.	
T3–T4	0.789 (0.625–0.997)	0.047	0.863 (0.677–1.101)	0.248	5.248 (2.550–10.799)	0.000	2.593 (1.135–5.922)	0.024
N stage								
N0	Ref.				Ref.		Ref.	
N1–N2	0.976 (0.766–1.244)	0.845			2.149 (1.078–4.284)	0.030	2.295 (1.061–4.966)	0.035
BLADE scoring system								
0	Ref.		Ref.		Ref.		Ref.	
1	1.581 (1.145–2.183)	0.005	1.408 (1.013–1.955)	0.042	3.389 (1.230–9.343)	0.018	3.221 (1.144–9.072)	0.027
2	3.150 (2.245–4.420)	0.000	2.423 (1.702–3.450)	0.000	9.100 (3.084–26.856)	0.000	6.261 (1.880–0.851)	0.003

BMI, body mass index; BLADE, blood loss and duration of excision.

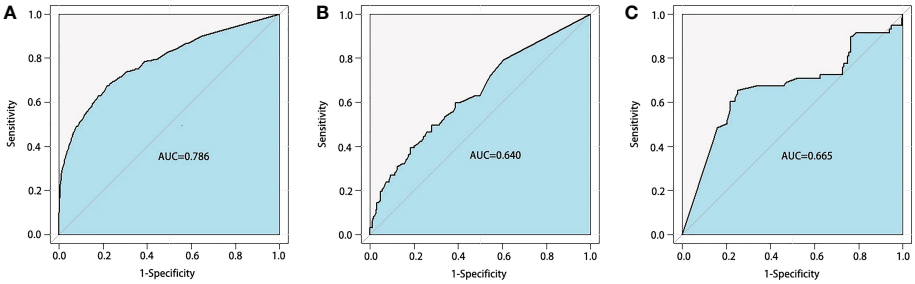

FIGURE 3
Receiver operating characteristics curves of random forest model for BLADE scoring system. The areas under the curve (AUCs) were 0.786 in the training set **(A)** 0.640 in the test set **(B)** and 0.665 in the external validation set **(C)** BLADE, blood loss and duration of excision.

surgical difficulty and influencing factors cannot be completely linear. Machine learning algorithms could effectively overcome the shortcomings of traditional methods, which can be used as a more accurate and non-linear tool to predict the outcomes of patients (46, 47). They can easily incorporate a large number of variables, as all calculations are performed using a computer to offer insights into latent interactions between numerous input features and output results to achieve output prediction (48). In the field of prediction, machine learning techniques are increasingly used in various areas including outcome prediction (49), but not in surgical difficulty prediction. The approach of machine learning is independent of complex interactions, which could lead to higher prediction accuracy. Therefore, we developed models using machine learning techniques to predict the difficulty of tLAR. This study demonstrated that the use of machine learning models can accurately predict the difficulty of tLAR. The results showed that the RF model presented a better performance for the prediction of the difficulty of tLAR than the other models. We also externally validated the models in a large cohort in which patient characteristics were broadly similar to the original derivation dataset, thus enabling a head-to-head comparison of the models. Notably, what is different from usual was that the predictive model performed better in the external validation dataset than in the internal validation cohort, which indicated that our predictive tool had the ability to identify surgical difficulty grades.

There are several limitations in this study. First, because a retrospective analysis was used, there are relatively heterogeneous data regarding the determination of tumor location based on different imaging protocols, surgical technique selection of tLAR, and the skills and experiences of surgeons. Second, pelvimetry in pelvic MRI plays an important role in determining the surgical difficulties of anterior resection. However, the information with regard to MRI was missing in the database, which could not be analyzed in this study. Third, the surgeon's experiences have been considered a key influencing factor for surgical difficulty, but we cannot calculate the influence of the surgeon's experience on this scoring system due to the lack of relevant information in this database. Fourth, the establishment and evaluation of the surgical difficulty grading system in anterior resection varied obviously between studies, which are unavailable for the comparison of our grading score with the others. Fifth, the subjectivity of the definition of surgical difficulty remains largely unaddressed, which likely leads to potential bias and makes the relationship between surgical difficulty and clinical outcomes difficult to explain. Despite the retrospective nature and limitations in the present study, the advantages of this study include that the surgical difficulty score grading of tLAR is established based on a large sample size of RC patients, and further investigations of the current scoring system should be performed with internal cohort and independent external cohort to validate the outcomes.

Conclusions

The easy-to-use BLADE score appears to be effective in predicting the short-term outcome for patients who are candidates to receive tLAR, convenient in making surgical plans for RC patients, and significant in promoting more studies for tLAR in both multicenter studies and randomized clinical trials in the near future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional review board of China National Cancer Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JFL: methodology, software, data curation, and writing—original draft preparation. XG: conceptualization, writing—original draft preparation, and data curation. RW: software. YFY: data curation. ERL: software. ZXZ: visualization. HPC: investigation. ZL: resources. ZJ: resources. XSW: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1067414/full#supplementary-material

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EDITED BY
Zhibo Yan,
Qilu Hospital, Shandong University, China

REVIEWED BY
Stefan Sauerland,
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Germany
Michael Grayling,
Janssen Pharmaceuticals, United Kingdom

*CORRESPONDENCE
Artur Rebelo
artur.rebelo@uk-halle.de

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Is it feasible and ethical to randomize patients between surgery and non-surgical treatments for gastrointestinal cancers?

Artur Rebelo*, Johannes Klose, Jörg Kleeff and Ulrich Ronellenfitsch

Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Halle, Germany

Background: In several settings in the treatment of gastrointestinal cancers, it is unclear if the addition of surgery to a multimodal treatment strategy, or in some circumstances its omission, lead to a better outcome for patients. In such situations of clinical equipoise, high-quality evidence from randomised-controlled trials is needed to decide which treatment approach is preferable.

Objective: In this article, we outline the importance of randomised trials comparing surgery with non-surgical therapies for specific scenarios in the treatment of gastrointestinal cancers. We explain the difficulties and solutions of designing these trials and recruiting patients in this context.

Methods: We performed a selective review based on a not systematic literature search in core databases, supplemented by browsing health information journals and citation searching. Only articles in English were selected. Based on this search, we discuss the results and methodological characteristics of several trials which randomised patients with gastrointestinal cancers between surgery and non-surgical treatments, highlighting their differences, advantages, and limitations.

Results and conclusions: Innovative and effective cancer treatment requires randomised trials, also comparing surgery and non-surgical treatments for defined scenarios in the treatment of gastrointestinal malignancies. Nevertheless, potential obstacles to designing and carrying out these trials must be recognised ahead of time to avoid problems before or during the trial.

KEYWORDS

cancer, randomized control trial (RCT), ethical, gastrointestinal, oncology

Introduction

In several settings in the treatment of gastrointestinal cancers, the available data cannot answer the question whether surgery or non-surgical treatments lead to a better outcome for patients. In such situations of clinical equipoise, to provide a valid answer to this question, as for any treatment recommendation in medicine, high-quality evidence is needed. Despite improvements in the quality of clinical research in surgical oncology, several aspects regarding the design of studies comparing surgery to no surgery are still a problem. Only some surgical treatments have been assessed in randomised controlled trials (RCTs), and a relevant proportion of surgical treatments is based on scarce and conflicting evidence (1). Practical and personal experience drives the apparent progress in surgery to a much higher extent than in drug treatments. Surgical RCTs represent only 15% of the published RCTs, and only about 24% of surgical therapies are supported by evidence from RCTs (2–4). A large proportion of published studies in surgical oncology have a retrospective observational design with several limitations and inherent risk of bias. Despite of recent efforts in designing surgical RCTs, in a systematic review of 388 randomised clinical trials, the sizes of surgical trials were small (5). Also, discrepancies with the published protocol and reporting bias were frequent (6–11). Randomising patients between additional surgery and no surgery involves confronting several problems: commercial interests in the light of high reimbursements for many surgeries, lack of cooperation between surgical and non-surgical departments, hesitancy and ethical concerns of patients and investigators to randomise between surgery and non-surgical treatments with the knowledge that surgery is a viable option, and blinding of patients and surgeons.

In this article, we outline the importance of conceiving randomised trials comparing surgery with non-surgical therapies for specific scenarios in the treatment of gastrointestinal cancers, highlighting the difficulties and solutions of designing these trials and recruiting patients in this context.

Why do we need randomization between surgery and non-surgical treatments?

An RCT has several advantages. The prospective nature of the study implies a planned assessment, documentation, and follow-up (1). The blinded RCT provides the highest level of evidence in evidence-based medicine and minimizes bias. Randomization is the best design to establish causal relationship between exposure and outcome. Non-randomized comparative cohort studies provide important data, but only with statistical adjustments (a. e. propensity score analysis) from covariates, an association between intervention and outcome may be shown, and a considerable risk of bias persists.

Regarding RCTs comparing surgery and non-surgical treatments, different types of comparison groups are possible: no active intervention, medical management, deferred surgery, active monitoring ("watch and wait"), physical or manual therapy and placebo (sham surgery).

In a systematic review comparing quality domains in trials of surgical interventions to a previously reported control sample of trials of medical interventions, although reporting of quality domains was suboptimal, surgical trials compared favorably to medical trials (12). "*They were 24% more likely to have an adequate method of random sequence generation, and 71% more likely to have an adequate method of allocation concealment. However, blinding was 40% less likely to be adequate in surgical trials, and sources of funding were 33% less likely to be reported*" (12). Although it is not a specific limitation of RCTs, publication bias is also a problem that has to be faced when designing these trials. Selective outcome reporting is a known problem of RCTs (10). For example, in neurosurgery, it was shown that RCTs comparing surgical to non-operative treatment fairly frequently changed their outcome measures, which may distort the available results of a given trial und undermines the trials' credibility (13).

Randomized controlled trials comparing surgery with non-surgical treatments are rare, but with the development of new multimodal therapy regimens in gastrointestinal cancer surgery, randomized comparisons of different medical and surgical approaches are needed (14). For example, conversion surgery is defined as an operation aiming to clear all tumor sites after tumors that had initially been considered technically unresectable or where a resection was deemed to be of no oncological benefit, responded to chemotherapy and become resectable (15). Another example is the possible omission of surgery after very good response to chemotherapy or chemoradiotherapy, as it is now discussed regarding complete response after total neoadjuvant therapy for rectal cancer (16).

Advantages and disadvantages of non-randomized trials

Usually, observational studies have some advantages when compared to RCTs: lower cost, greater timeliness, and a broader range of patients eligible for study inclusion. Despite its limitations on comparing treatments, they are used to identify risk factors and prognostic factors (17). Furthermore, in some clinical scenarios, non-randomized prospective cohort studies categorizing and comparing observational data may represent better alternatives than RCTs (18–21). These types of studies potentially lead to a higher participation of the patients in the interventional group, mostly according to the preferences of the clinician or the patient. Despite of the risk of selection bias, these studies give insights on the outcomes of the effects of surgical treatments and provide, in some cases, quality evidence comparable to RCTs. The level of evidence gained from a poor quality RCT is not necessarily better than that from a well-conducted cohort study. *A priori* registration of protocols is still not required in observational studies but would be a major strength to avoid explorative data analyses. Conducting and reporting observational studies according to the Strengthening

the Reporting of Observational studies in Epidemiology (STROBE) Statement is a requirement for publication in some journals (22). Nevertheless, prospective observational studies usually represent complementary evidence or are the basis for designing RCTs (23, 24). Chalmers et al. reported that 56 percent of non-randomized trials reported on favorable treatment effects, as compared with 30 percent of blinded, randomized-controlled trials. This potential selection bias was also reported in other studies (25–28).

As demonstrated, the potential for bias in RCTs is normally lower when compared to non-randomized studies. Bias is defined as the systematic difference between the study results and an RCT, addressing the same question and conducted on the same participant group that had no flaws in its conduct. Assessing bias of a non-randomized study involves comparing it to a hypothetical pragmatic RCT that compares the health effects of the same interventions and is conducted in the same participants without features putting it at risk of bias. The assessment of risk of bias in non-randomized studies involves pre-intervention, at-intervention, and post-intervention features of the study (29, 30). The bias related to non-random allocation results in over- or underestimations of treatment effects, being large enough to lead studies to false conclusions. Even when applying case-mix adjustment methods (i. e. logistic regression, propensity score) bias stays significant (31). The absence of reliable methods to prevent the biasing consequences of selection bias in observational research leaves non-randomized studies for situations when RCTs are unfeasible or unethical. Unfeasibility of RCTs usually is present when the disease or indication is very rare, and ethical problems often arise when very large treatment effects can already be seen in non-randomized studies, so that equipoise can no longer be assumed (32).

Disadvantages of randomized trials

Surgical trials are difficult to conceive, and only half of the initiated trials reach their recruitment target (33–35). When performing these studies, surgical clinician scientists face several obstacles such as the surgical learning curve and the lack of financial support. Furthermore, blinding problems, poor generalizability of the trial population and difficulties with randomization in emergency situations represent important adversities that researchers must overcome. These and other problems result in 21% of RCTs in surgery being discontinued and 34% being unpublished (36, 37)

Surgical trials face patient and surgeon related challenges: a radical choice between treatments, patients' discomfort with randomization between an operation and no operation, patients' or clinicians' *a priori* preferences for one or the other treatment, and an imbalanced presentation of the treatment options to patients (38). Regarding trials comparing surgical and non-surgical interventions, slow recruitment is mentioned to be the most common problem that researchers have to confront, with the consequence that no evidence-based treatment recommendations can be made (39–42).

Furthermore, historical and cultural limitations are relevant when designing RCTs comparing surgery with non-surgical treatments. Most surgical treatments were developed to treat conditions that were untreatable with other means and were potentially life-threatening. Once a surgical treatment is established, it is difficult and sometimes appears ethically questionable to compare it to a medical treatment or surveillance. Structural, political, and commercial aspects also play an important role. Regarding ethical aspects, the possible adverse effects of surgery and non-surgical treatments usually differ substantially, and surgery is mostly irreversible with organs or parts thereof being removed. Due to these limitations, an indirect selection bias may be present in these RCTs, as only a small subgroup of patients may agree to participate on them.

Placebo controlled trials represent another option in this context. In the context of surgery, placebo means sham surgery, i.e. general anesthesia without an actual operation, or a surgical procedure intended to mimic the actual operation. However, the conception of a placebo control in a surgical RCT may be challenging and ethically difficult because the surgical unlike the medical "placebo" bears a relevant degree of invasiveness. If there is no expected benefit (beside the placebo effect), patients are usually resistant to undergo the low-risk anesthesia required for a sham surgery intervention. Blinding is also very difficult in this kind of trials. Nevertheless, surgical RCTs with a placebo arm are feasible, with the recruitment of patients remaining the leading challenge (43).

Advantages of randomized trials

Notwithstanding the challenges outlined above, randomized-controlled trials remain the gold standard for generating evidence on what is the best treatment for a given condition or in a specific setting. This holds equally true with regard to both medical treatments as well as surgical procedures and is of particular importance for patients with gastrointestinal cancers, where the choice of treatment has direct implications on survival, treatment-related morbidity and mortality, and quality of life, among other outcomes. Therefore, all reasonable efforts should be made to design and carry out randomized-controlled trials also for comparing surgical treatments with no surgery in patients with gastrointestinal cancers. Motivating patients for enrolling into such trials requires open, patient-centered, and evidence-based communication. Only by thoroughly explaining all expected risks and benefits, both in terms of procedural and long-term oncological outcomes, in an impartial way, patients can be empowered to make an informed decision on trial participation, which will ultimately enhance the probability of enrollment (44, 45). In a situation of assumed clinical equipoise, which is the foundation of all RCTs, surgery should neither be regarded only as a chance for cure or prolongation of life without appreciating its associated risks nor as a mere invasive procedure with morbidity and mortality risks without considering possible beneficial effects on oncological outcomes like survival. Quality of life, which can possibly be affected in both a

positive and negative direction by a surgical procedure, is of high importance for many patients when deciding for or against surgery and must be specifically addressed in such conversations (46). Pre-existing preferences of patients towards one or the other treatment need to be considered, addressed openly and discussed using available evidence (47). The general advantages of participating in a controlled clinical trial, such as close monitoring, possibly more frequent follow-up visits and access to novel treatments, need to be well explained to patients, but should not be overstated in a promotional manner (48). While discontinuation of the trial by single patients should obviously not be encouraged, the freedom of choice to quit trial participation at any time, and eventually even to seek the alternative treatment, i.e. surgery for patients who had been randomized into the no surgery arm or no surgery for patients who had been randomized into the surgery arm (as long as the operation has not been carried out) should be addressed, too. "Placebo"-controlled trials are almost impossible to realize in surgical oncology. Sham surgery, which would potentially delay further non-surgical treatments such as chemotherapy, seems ethically not acceptable for cancer patients. Sham anesthesia could be a theoretical less invasive option, but a lack of scars would still render long-term blinding of patients not feasible. Therefore, RCTs in surgical oncology including those enrolling patients with gastrointestinal cancer are usually open-label studies.

Given that the likelihood of selective participation in RCTs randomizing between surgery and no surgery based on patients' characteristics is considerable, efforts should be made to collect baseline but also outcome data from patients who are screened and offered trial participation, but who ultimately choose not to enroll. Observational cohorts comprising patients who refused trial participation or did not meet all inclusion criteria but were treated with identical interventions as if they had participated in the respective trial, can support evidence generated by RCTs. In a specific example of an RCT comparing preoperative radiotherapy plus surgery with surgery alone in patients with retroperitoneal sarcoma, results from such an observational cohort closely resembled the results from the actual RCT (49).

Another possible solution is the use of adaptive randomized trial designs. This allows modifications to the trial design during the collection of patient outcome data and despite its challenges, may present several advantages when compared to standard trial designs (50).

Examples of successful randomization between surgery and non-surgical treatments

Several examples show that RCTs comparing surgery and no surgery in specific treatment settings of gastrointestinal cancers can be successfully conducted.

In a potentially curative setting, the FFCD 9102 trial randomized patients with thoracic esophageal squamous cell carcinoma or adenocarcinoma who had shown clinical response to neoadjuvant chemoradiotherapy to either resection or continuation of chemoradiotherapy (51). Only 14 of 273 patients (5.1%) fulfilling all eligibility criteria refused randomization. Compliance with the allocated treatment was high with only 10 of 129 patients (7.8%) randomized to surgery deciding against the operation and only 1 of 130 patients (0.8%) randomized to continuation of chemoradiotherapy demanding surgery. A trial with a similar design randomized 37 of 38 eligible patients (97.4%) with squamous cell carcinoma of the esophagus, who showed complete clinical and metabolic response to chemoradiotherapy, to esophagectomy or observation (52). While all 18 patients allocated to observation were compliant with that treatment with some patients being operated on later because of secondary progression, 6 of 19 patients (31.6%) allocated to surgery chose not to have the operation. Overall enrolment into the trial was much slower than expected which together with the low compliance with treatment in the surgery arm led to premature trial closure. The trialists assumed that compliance of patients allocated to surgery was low due to the timing of randomization after complete response had been confirmed and with a general change of local treatment patterns towards observation instead of surgery. The ongoing RENAISSANCE trial randomizes patients with oligometastatic gastroesophageal adenocarcinoma and no disease progression following chemotherapy between additional chemotherapy or resection of the primary tumor and the metastatic lesions followed by chemotherapy (53). In a similar population, i.e. patients with gastric adenocarcinoma and one metastatic site, the REGATTA trial randomized between gastrectomy followed by chemotherapy and chemotherapy alone (54). All enrolled 175 patients were successfully randomized. While 7 of 86 patients (8.1%) allocated to chemotherapy alone withdrew consent, 1 of 89 (1.1%) patients allocated to gastrectomy plus chemotherapy decided not to undergo the operation.

In rectal adenocarcinoma, which often shows very good or even complete response to neoadjuvant chemoradiotherapy, several trials randomizing between rectal resection and organ preservation, either through a watch-and-wait strategy or local excision, have been or are being conducted. The GRECCAR-2 trial randomized 145 out of 146 eligible patients (99.3%) who demonstrated good response to chemoradiotherapy (55). Only 1 of 74 patients (1.4%) allocated to local excision underwent rectal resection while 8 of 73 patients (11.0%) allocated to rectal resection underwent local excision and 3 of 73 patients (4.1%) no surgery at all. In the TREC trial, 55 of 152 identified eligible patients (36.2%) consented to randomization between organ preservation by transanal microsurgery and radical rectal resection (56). Of the 27 patients allocated to organ preservation, 3 patients (11.1%) crossed over to the rectal resection arm, and one patient had to end protocol treatment because of metastatic disease. Of the 28 patients allocated to rectal resection, 3 patients (10.7%) refused surgery and crossed over to the organ preservation arm.

The SYNCHRONOUS trial randomized patients with colon cancer and unresectable synchronous metastases to resection of the primary before starting chemotherapy (187 patients) and chemotherapy without prior resection (206 patients). Results have

so far only been published in abstract form, and no information on the proportion of eligible screened patients who were randomized and on compliance with the allocated treatments are available (57).

A Chinese trial randomized patients with metastatic gastrointestinal stromal tumor responding to imatinib treatment either to surgery of residual disease followed by continuation of imatinib treatment or to continuation of imatinib treatment without surgery (58). Although only 5 of 46 screened eligible patients (10.9%) refused entering the trial, the trial had to be closed prematurely due to slow accrual. However, all patients received the treatment they were allocated to with no crossing over or refusal of therapy.

Conclusions

As in all other fields of medicine, guidelines, and recommendations for when and if surgery for gastrointestinal cancers should be performed need to be based on evidence of the highest possible level. Such evidence can only be provided by well-designed RCTs with other study designs bearing a non-negligible risk of bias, which compromises the validity of their results. A randomization between an operation and no operation with either a watch-and-wait approach or an alternative non-surgical treatment is ethically fully acceptable if there is clinical equipoise between the two treatments. However, it is often more difficult for patients and physicians to accept than a randomization between two drugs or even between a presumably active drug and a placebo. Frequently, there is an *a priori* preference towards either the surgical treatment or against surgery, even if such preferences are not supported by available data. A dedicated explanation of all expected risks and benefits associated with trial participation, and the open discussion of patients' pre-existing preferences are key factors for achieving fast and unselected recruitment into these RCTs. Several trials conducted in esophageal cancer and colorectal cancer show that randomization between surgery and no surgery or microsurgery can be successfully done both in a setting with curative intent and in metastatic disease. These examples should be encouraging for researchers to conceive of, design, and carry out more of these RCTs to provide high-level evidence for unanswered treatment questions for gastrointestinal cancers.

Author contributions

AR, JKlo, JKle and UR performed research, selected manuscripts wrote and edited the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Jorg Kleeff,
University Hospital in Halle, Germany

REVIEWED BY
Rita Alfieri,
Veneto Institute of Oncology (IRCCS), Italy
Noel Donlon,
Trinity College Dublin, Ireland

*CORRESPONDENCE
Ying Zhang
270346831@qq.com
Gang Ji
Jigang@fmmu.edu.cn
Xiaohua Li
xjyylixiaohua@163.com

†These authors have contributed equally to this work

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Comparison of thoracoabdominal versus abdominal-transhiatal surgical approaches in Siewert type II adenocarcinoma at the esophagogastric junction: Protocol for a prospective multicenter randomized controlled trial

Chao Yue[1†], Zhenchang Mo[2†], Xiao Wu[1†], Yannian Wang[1†], Qinchuan Yang[1], Weidong Wang[1], Haikun Zhou[1], Ruiqi Gao[1], Panpan Ji[1], Danhong Dong[1], Ying Zhang[3*], Gang Ji[1*] and Xiaohua Li[1*]

[1]Department of Gastrointestinal Surgery, Xijing Hospital, Air Force Medical University, Xi'an, Shaanxi, China, [2]Department of Oncology, Affiliated Hospital, Shannxi University of Chinese Medicine, Xianyang, Shannxi, China, [3]Department of Radiotherapy, Xijing Hospital, Air Force Medical University, Xi'an, Shaanxi, China

Background: Siewert type II adenocarcinoma of the esophagogastric junction (Siewert II AEG) can be resected by the right thoracoabdominal surgical approach (RTA) or abdominal-transhiatal surgical approach (TH) under minimally invasive conditions. Although both surgical methods achieve complete tumor resection, there is a debate as to whether the former method is superior to or at least noninferior to the latter in terms of surgical safety. Currently, a small number of retrospective studies have compared the two surgical approaches, with inconclusive results. As such, a prospective multicenter randomized controlled trial is necessary to validate the value of RTA (Ivor-Lewis) compared to TH.

Methods: The planned study is a prospective, multicenter, randomized clinical trial. Patients (n=212) with Siewert II AEG that could be resected by either of the above two surgical approaches will be included in this trial and randomized to the RTA group (n=106) or the TH group (n=106). The primary outcome will be 3-year disease-free survival (DFS). The secondary outcomes will include 5-year overall survival (OS), incidence of postoperative complications, postoperative mortality, local recurrence rate, number and location of removed lymph nodes, quality of life (QOL), surgical Apgar score, and duration of the operation. Follow-ups are scheduled every three months for the first 3 years after the surgery and every six months for the next 2 years.

Discussion: Among Siewert II AEG patients with resectable tumors, this is the first prospective, randomized clinical trial comparing the surgical safety of minimally invasive RTA and TH. RTA is hypothesized to provide better digestive tract reconstruction and dissection of mediastinal lymph nodes while maintaining a high quality of life and good postoperative outcome. Moreover, this trial will provide a high level of evidence for the choice of surgical procedures for Siewert II AEG.

Clinical trial registration: Chinese Ethics Committee of Registering Clinical Trials, identifier (ChiECRCT20210635); Clinical Trial.gov, identifier (NCT05356520).

KEYWORDS

adenocarcinoma of the esophagogastric junction, Siewert type II, thoracoabdominal, abdominal-transhiatal, surgical approaches

Background

Adenocarcinoma of the esophagogastric junction (AEG) is defined as a tumor with an epicenter within 5 cm of the esophagogastric junction (EGJ) (1). Over the past two decades, the incidence of AEG has increased significantly, accounting for 5-8% of esophageal cancer in China and 35.7% of gastric cancer and lower esophageal cancer around the world (2–4). Siewert and Stein divided AEGs into three categories based on the distance between the tumor center and the EGJ. The epicenter of a tumor that measures between 1 and 5 cm above the EGJ is defined as type I, while that of an epicenter within 1 cm above and 2 cm below the EGJ is defined as type II, and those within 2–5 cm below the EGJ are defined as type III (5).

Currently, AEG is treated mainly by surgical resection. The National Comprehensive Cancer Network (NCCN) guidelines state that the management of Siewert type I should be similar to that of esophageal cancer, and the thoracoabdominal surgical approach (TA) is recommended because of its higher rate of thoracic lymph node involvement. Siewert type III should be managed as gastric cancer, and an abdominal-transhiatal surgical approach (TH) is recommended (6, 7). However, Siewert type II adenocarcinoma of the esophagogastric junction (Siewert II AEG) differs from the other two types in terms of its anatomical location and biological behavior, which is characterized by high differentiation, deep invasion, susceptibility to metastasis and adverse outcomes (8), making the proper operative approach for Siewert II AEG controversial.

To provide the most effective surgical treatment strategy for patients with Siewert II AEG, the ideal approach should not only consider primary tumor removal and local lymph node dissection but also ensure a safe and effective digestive tract reconstruction method (9). At present, some specialists prefer TA, while others prefer TH (10–12). Compared with TH, TA has a better effect on mediastinal lymph node dissection, with significant advantages for the dissection of subcarinal, paraesophageal, hilar and diaphragmatic lymph nodes (13). And TA provides more operating spaces for resection of the distal esophagus, which ensures a long enough upper resection margin distance from the tumor (10). However, TH can avoid invasion of the chest and minimize pleural complications, which is superior to transthoracic surgery in this respect. In addition, the surgical approach to TA varies in different countries. In Western countries, the right thoracoabdominal surgical approach (RTA) is preferred, whereas in Asian countries, the left thoracoabdominal surgical approach (LTA) is preferred. The results of a prospective study comparing the LTA and RTA showed that the overall number of lymph nodes removed during the LTA was inferior to the RTA, especially for abdominal lymph nodes (14). Further comparison of long-term survival studies showed that the 3-year DFS, OS and local recurrence rate of the RTA were better than those of the LTA (15). Therefore, the NCCN guidelines recommend the RTA rather than LTA for patients with Siewert II AEG (6). Nevertheless, studies have shown that thoracoscopic surgery has a higher incidence of respiratory and cardiovascular complications (16). A meta-analysis including 16 studies indicated that significantly higher incidence of cardiovascular and respiratory complications, and longer length of hospital stay were observed in the RTA group (17). As a result, RTA has certain limitations compared with TH. Thankfully, extensive use of thoracoscopy and laparoscopy in recent years could provide better surgical views and more space for radical surgery of esophagogastric junction Siewert-type adenocarcinoma. A minimally invasive surgical approach can significantly lower the incidence of cardiovascular and respiratory diseases, at the same time reduce intraoperative blood loss, speed up recovery of bowel function and contribute to early discharge compared to open surgery (18). Previous studies have shown that both the minimally invasive Ivor Lewis (RTA) procedure and the

Abbreviations: AEG, Adenocarcinoma of the esophagogastric junction; EGJ, Esophagogastric junction; Siewert II AEG, Siewert type II adenocarcinoma of the esophagogastric junction; RTA, Right thoracoabdominal; LTA, Left thoracoabdominal; TA, Thoracoabdominal; TH, Abdominal-transhiatal.

minimally invasive abdominal-transhiatal (TH) procedure are superior to open surgery in terms of safety and efficacy for patients with Siewert II AEG (19).

According to the study reported by Wee et al., the minimally invasive RTA approach mainly includes laparoscopic partial or total gastric resection, followed by thoracoscopic distal esophagotomy and mediastinal lymph node dissection (20). The study identified minimally invasive RTA as a viable and safe surgical approach with significantly lower morbidity and mortality compared to open surgery. And Wang et al. reported that minimally invasive TH approach would only be performed by laparoscopy for gastrectomy, distal esophagectomy and diaphragmatic hiatus mediastinal lymph node dissection (19). They believe that minimally invasive TH approach is also a safe and feasible approach with great prospects for clinical application. To date, there are no prospective randomized controlled trials comparing RTA with TH under minimally invasive conditions. Therefore, whether minimally invasive RTA is better than minimally invasive TH is of great research value for the improvement of clinical therapeutic effects for patients with Siewert II AEG.

Based on these points, it is necessary to compare surgical safety, oncology outcomes, and quality of life between RTA and TH for patients with resectable Siewert II AEG in a multicenter randomized controlled trial.

Methods

Objective

The purpose of this trial is to compare RTA with TH for resectable Siewert II AEGs based on surgical safety, clinical efficacy and prognosis. The primary outcome of the study will be the 3-year disease-free survival (DFS) to assess the oncological safety of the procedure. The secondary outcomes will be 5-year overall survival (OS), incidence of postoperative complications, postoperative mortality, local recurrence rate, number and location of removed lymph nodes, surgical Apgar score, duration of the operation and the quality of life (QOL) score.

Study design

This is the first prospective multicenter randomized clinical trial comparing the efficacy of RTA and TH, which will be carried out in China. Centers participating in the trial will include Xi-jing Hospital, Tang-du Hospital, Henan Province People's Hospital, General Hospital of Ningxia Medical University, First Affiliated Hospital of Xi 'an Jiaotong University and the First Affiliated Hospital of Shanxi Medical University. The Declaration of Helsinki statement, as well as the international ethical guide to human biomedical research, form the guiding principles of this research. This study has been registered at clinical-trial.gov (NCT05356520) and approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20210635). Upon modification of the protocol, the participating institutes will be notified, and the ethics committee will need to approve it again if the change substantially affects the trial. Surgeons who are competent in both approaches will conduct this study. Throughout the study, surgeons, patients, and coordinating researchers will not be blinded to the group allocation.

Study population

This trial will evaluate patients with Siewert II AEG whose tumors can be safely resected by both minimally invasive RTA approach and minimally invasive TH approach.

The inclusion criteria for this study are as follows

- ·Siewert II AEG confirmed histologically
- ·Both RTA and TH can safely resect the tumor
- ·Pretreatment stage $cT_{1\text{-}4a}$, $N_{0\text{-}3}$, M_0 (referring to the 8th AJCC TNM staging system)
- ·Aged 18-75
- ·The Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 2
- ·American Society of Anesthesiologists (ASA) <4
- ·Laboratory tests: hemoglobin > 90 g/L, white blood cells > 3×10^9/L, platelet > 100×10^9/L, glomerular filtration rate > 60 ml/min, total bilirubin < 1.5x upper level of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5x ULN
- ·Informed consent is voluntarily signed by the patients and their families

The exclusion criteria are as follows

- ·Siewert type I and III adenocarcinoma of the esophagogastric junction confirmed histologically
- ·A tumor that extends more than five centimeters from the EGJ or has developed distant metastases (M1) or peritoneal invasion
- ·Significant cardiovascular disease, such as coronary atherosclerosis or myocardial infarction, with symptoms in the past 6 months
- ·Significant respiratory disease, defined by whether the forced expiratory volume in 1 second (FEV1) is less than 1.5 L/s
- ·History of right thoracotomy, adhesions to the right pleura or prior epigastric surgery
- ·Indocyanine green test is not less than 15% for significant cirrhosis or chronic liver disease

·Overt central nervous system disorders, mental disorders, and psychological disorders
·Significant coagulopathy that has not been modified by current technology
·Significant endocrine disorders, such as uncontrolled diabetes
·A disease that is seriously out of control, such as a recurrent infection
·Tumor-related diseases that require emergency surgery due to special conditions such as bleeding, perforation and obstruction

The termination test standards are as follows

Patients will be terminated if any of the following conditions occur, and the study analysis will not include data from these individuals:

·Patients who are found to be inoperable for a variety of reasons after trial registration (the reasons should be documented in detail)
·The investigator considers the patient unfit for further participation in the study (reasons for withdrawal should be recorded in detail)
·The patient requests termination of the trial
·The patient violates the treatment principles (violating the admission criteria, disobeying the study arrangements, etc.)

Patient screening

Figure 1 displays the trial flow. Before enrolling a patient, a comprehensive assessment will be performed to determine whether the patient meets the enrollment criteria. The results of the endoscopy and pathological analysis will be used to determine whether the classification criteria of Siewert II AEG are met. CT, enhanced CT, MRI, PET-CT and endoscopy will be used to identify and judge the tumor infiltration depth and the possibility of distant metastasis. A physical examination and laboratory tests for the patients are also essential screening methods. In addition, the medical history and basic demographics should be included in the complete preoperative work-up.

Patient inclusion and randomization

After all of the patients have completed the baseline assessment, they will be reviewed on a case-by-case basis according to the trial's inclusion and exclusion criteria. Subsequently, an opaque envelope will be unsealed by a research assistant who is not involved in the recruitment and review of patients. This envelope contains a random number table for randomly assigning people who meet the trial requirements to either the RTA or TH group. The patients and surgeons cannot be blinded to their assignment, whereas the pathologists will be blinded to the patient's group assignment.

Patient follow-up

According to the schedule (Table 1), the patients will be followed for the first time one month after surgery and then every three months for three years. An additional follow-up survey of the indicators will be conducted semiannually for the next two years. All patients will be required to be followed for at least five years. Each follow-up will include a physical examination, a routine blood examination and a serum tumor marker examination every three or six months. Enhanced thoracic and abdominal CT will be performed every six months, and gastroscopy will be performed annually. If a tumor recurrence or metastasis is suspected, additional tests will be performed and recorded on the CRF table. Trial-related complications will be assessed based on the Clavien –Dindo classification. If grade III or above complications occur, they will be reported to the responsible unit of the project, fed back to the study supervision department, and comprehensively evaluated to how to deal with this situation in time and effectively. All follow-up will be performed by the project's professional follow-up team. The trial will be completed until the last patient completes their follow-up.

Intervention

An equal number of patients will be randomly assigned to the RTA and TH groups. Details of the surgery are determined by the surgeons at each center as long as the tumor can be resected completely. If the tumor is difficult to be resect under minimally invasive conditions, the surgical strategy will be adjusted at that time.

The TH approach will be performed by distal esophagectomy and mediastinal lymph node dissection *via* the diaphragmatic hiatus under laparoscopy, whereas the RTA approach will be performed under thoracoscopy. The resection margin is a key indicator for evaluating the curative effect of surgery. The 5-year mortality of patients with positive resection margins is significantly higher than that of patients with negative resection margins (21).

According to the NCCN guidelines (6) and the Chinese expert consensus, for Siewert type II AEG with cT1 stage, the upper esophageal resection margin is recommended to be at least 2 cm away from the tumor, while for patients with cT2 stage or above, the upper esophageal resection margin is recommended to be at least 5 cm away from the tumor if the RTA approach is performed and at least 3 cm if the TH approach is performed. For patients in the former staging category, the lower resection margin is recommended to be at least 3 cm, while for patients in the latter staging category, a minimum of 5 cm is required to meet the surgical requirements. Laparoscopic proximal gastrectomy can be performed regardless of the surgical

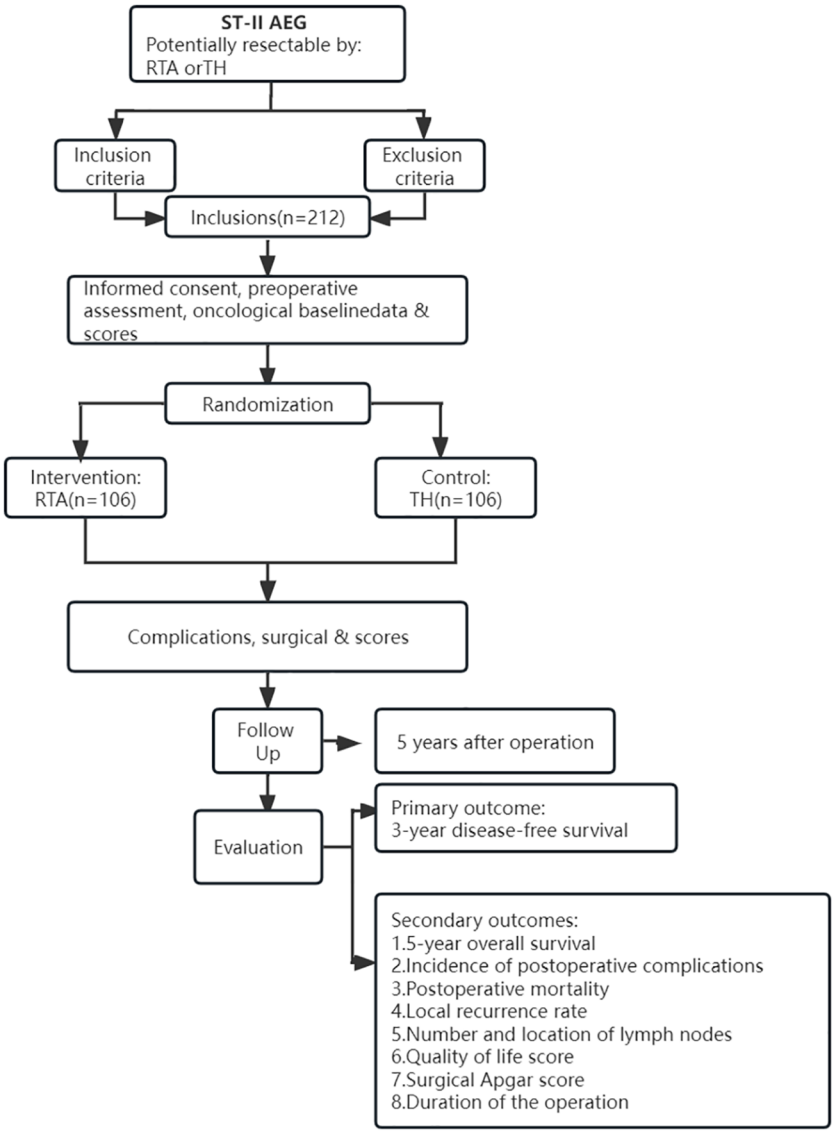

FIGURE 1
Flow chart.

approach if the above criteria for the lower resection margin are met and at least more than half of the residual stomach remains.

In addition, total gastrectomy with D2 lymphadenectomy is recommended if the tumor involves more than 4 cm of the stomach. Lower mediastinal lymph node dissection is generally not required when the tumor is less than 2 cm away from the esophagus but is required when it is 2 cm or more. It is important to note that dissection of the upper, middle, and lower mediastinal lymph nodes is recommended once the tumor has invaded the esophagus at a distance of 4 cm or more. Postoperative reconstruction of the digestive tract will be determined by the surgeon's personal experience and the patient's situation. Proximal gastrectomy is feasible with gastric tube reconstruction and esophagogastrostomy. Roux-en-Y (esophagojejunostomy and jejunojeju-nostomy) reconstruction is recommended for total gastrectomy. In addition, minimally invasive surgery might need to be converted to open surgery if complications arise during the surgery. And participants may discontinue their participation at any time during the study.

Surgical quality control

Each center must be a tertiary hospital that has performed at least 20 minimally invasive RTAs and 20 THs in each of the past three years. Surgeons who are skilled in both procedures and have performed each procedure at least 20 times will be eligible for the trial. To ensure surgical quality and facilitate whole-course monitoring, photographs should be taken during each operation to show the integrity of lymph node dissection and tumor resection. If the R0 resection rate is found to be low or the effect of dissected

TABLE 1 Checklist for collection of necessary clinical data and follow-up schedule of enrolled patients.

	Baseline information				Follow-up (months)																
	Preoperation	Operation	POD 1-7	Discharge	1	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Demography	√																				
Informed consent	√																				
Medical history	√																				
Oncological history	√																				
Tumor classification	√																				
Biometric data	√																				
Laboratory	√						√		√		√		√		√		√	√	√	√	√
Physical examination	√				√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Inclusion / Exclusion	√																				
Randomisation	√																				
Anamnesis	√				√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Gastroscopy	√								√				√				√		√		√
Enhanced thoracic and abdominal CT	√						√		√		√		√		√		√	√	√	√	√
Abdominal ultrasound	√						√		√		√		√		√		√	√	√	√	√
Concomitant Medication	√			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Surgical information		√																			
Pathology				√																	
postoperative complications			√	√	√																
postoperative mortality			√	√	√																
local recurrence rate				√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
surgical Apgar score		√																			
SF-36	√			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
EORTC QLQ-C30	√			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
EORTC QLQ-OES18	√			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

(Continued)

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TABLE 1 Continued

	Baseline information				Follow-up (months)																			
	Preoperation	Operation	POD 1-7	Discharge	1	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60
Disease-free survival					√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Overall survival					√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

√, Indicates the need to collect the clinical data

SF-36, Short-Form 36; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-OES18, Computerized adaptive test European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Esophageal cancer.

lymph nodes cannot meet requirements during the monitoring process, it will be necessary to analyze the problems and determine the possible reasons.

Pathological quality control

For the pathological examination to be of high quality, all samples from lymph node stations and peritumoral stations will be examined and analyzed by the pathology department. The surgeon will pack every lymph node station during the lymph node dissection, allowing the pathologist to examine the station individually. In contrast, the peritumoral stations will be marked as a whole rather than individually resected to ensure that the margin of resection can be accurately analyzed. Each center's lead pathologist will review the slides of ten percent of all cases. Except for the tissue for pathological analysis, which needs to be stored in wax blocks for 30 years, the rest of the tissue samples submitted for examination will be destroyed prior to pathological analysis, while all blood samples will be destroyed after pathological analysis.

Postoperative treatment

There will be no difference in postoperative treatment between the two groups. Analgesia and antibiotics will be administered according to the standards of each trial site. The surgeons at each participating institution will be responsible for implementing postoperative fluid rehydration and nutritional support. Patients with advanced AEG will routinely receive postoperative adjuvant chemotherapy. Each trial center will discharge patients in accordance with their standard practices.

Outcome measures

The primary outcome is a comparison of 3-year disease-free survival (DFS) between the two groups. The secondary outcomes of the trial included 5-year overall survival (OS), incidence of postoperative complications, postoperative mortality, local recurrence rate, the number of lymph nodes, quality of life (QOL) score, surgical Apgar score and duration of the operation. All types of postoperative complications will be defined by the Esophageal Complications Consensus Group (ECCG) (22) and classified by the Clavien–Dindo grading system (23). A variety of questionnaires will be used to assess QOL. General health aspects will be measured by the SF-36 and CAT EORTC QLQC30, whereas esophageal health will be assessed by the CAT EORTC QLQ-OES18 (24).

Data collection and management

The clinical data will be completely, timely, accurately and truthfully recorded in the CRF table by the study coordinator. Any changes that are made will be signed and dated by the person

concerned, but these changes will never involve the original data. Since randomization is centralized, each participating center will use thestratified-field block-randomization method (25). The study coordinator randomly assigned study populations meeting inclusion and exclusion criteria to either the RTA group or the TH group based on random numbers drawn from the hidden envelope. And each center will assign another study coordinator to be responsible for the data entry and uploading. The project sponsor or the clinical coordinator on behalf of the sponsor will be in regular contact with the center to provide information and technical support. In this way, the investigators can be supervised to strictly implement the study protocol, and to a certain extent, the accuracy of the clinical information on the CRFs can be verified. Authorized representatives of the project undertaking units, regulatory authorities, and ethics committees have the right to audit and inspect the works of each research center at any time, including original data verification. The purpose of an audit or inspection by the project undertaking unit is a comprehensive and targeted review of all study-related activities and documentation, which can guarantee that these activities are supervised in accordance with the guidelines of the research proposal and other regulatory requirements, and the clinical data are accurately analyzed, recorded and reported.

Sample size calculation

To calculate the required sample size, the primary outcome is taken into account. According to a previous retrospective study (26), the 3-year disease-free survival (DFS) is 47.6% for RTA and 32% for TH. Then, we calculated 212 patients (106 in the RTA group and 106 in the TH group) need to be enrolled in this trial using a one-sided two-sample t-test. The conventional type I error is 5%, the statistical power is 90%, and the dropout rate is 15%. Prior to participating in the trial, every center should report the number of patients likely to be recruited with reference to the number of patients admitted in recent years for Siewert II AEG.

Statistical analysis

Standard descriptive statistics will be used to analyze the qualitative and quantitative variables, including the relative and absolute frequencies, means, medians, standard deviations, and interquartile ranges. Continuous variables will be compared using Student's t-tests or Mann–Whitney U tests, while categorical variables will be compared using chi-square tests or Fisher's exact tests. A confidence of 95% will be considered suitable for analysis. Statistical significance will be defined as a p value of 0.05 or less. IBM SPSS (Version 28, Chicago, USA) will be used to conduct the statistical analysis.

Ethical approval and consent to participate

This is a prospective multicenter randomized controlled study aiming to identify the optimal surgical approach for Siewert II AEG. All legal requirements, regulations, and general principles of conduct in human biomedical research will be strictly followed in this study. In addition, the Declaration of Helsinki and the International Code of Ethics for Biomedical Research Involving Humans are essential principles guiding the conduct of this research. Clinical trials registered with the Chinese Ethics Committee have approved the research (Approval No. ChiECRCT20210635, 30 January 2022). The ethics committee is obliged to assess the progress of the research periodically and will be notified in case of any adverse events (AES).

Discussion

The incidence of adenocarcinoma at the esophagogastric junction (AEG) has increased from 22.3% to 35.7% in the last few decades (4). AEG is highly likely to recur and metastasize, which results in a poor outcome (27). Surgical resection is considered to be the main curative treatment with a favorable prognosis. As the minimally invasive techniques of laparoscopy and thoracoscopy are in widespread use, the choice of surgical methods has become more diverse. Lymph nodes may be dissected by various surgical approaches, which will have a strong impact on the prognosis. However, intense debate has raged for decades regarding the proper operative approach for AEG, especially for Siewert II AEG (8).

The previous literature has shown that the main surgical methods for Siewert II AEG include TH and TA (7). A 10-year follow-up of the JCOG9502 study in Japan showed that LTA was not only ineffective in improving overall or disease-free survival but also increased postoperative morbidity. Therefore, in cases of esophageal invasion depths under 3 cm in AEG type II tumors, they recommended avoiding the LTA approach. However, that study had some limitations, such as a failure to show survival differences between the two procedures, not including minimally invasive procedures, and using only LTA instead of the Ivor-Lewis approach (28).

In recent years, a large number of studies have shown that the LTA approach is inferior to the RTA in terms of the number of lymph nodes dissected, long-term survival, recurrence and prognosis, causing the LTA approach to fall out of favor (6, 14, 15, 29). Compared with the LTA approach, Blank et al. found that the RTA (Ivor-Lewis operation) had a significantly longer survival time than the TH approach. Multivariate analysis showed that the surgical type was an independent prognostic factor. Nevertheless, that study was a single-center, nonrandomized, controlled study that did not use minimally invasive surgery (10). In contrast, a single-center retrospective study found that the TH is more effective in achieving an optimal extent of lymph node dissection, reducing complications, shortening hospital stays, and promoting recovery (11). Although RTA has great advantages in mediastinal lymph node dissection, ensuring a negative esophagectomy margin and completing gastrointestinal reconstruction, it also invades the chest and increases the incidence of chest-related complications (10, 12).

With the introduction of laparoscopic fundoplication in 1991, minimally invasive surgical approaches have been noticed and accepted by a wide range of surgeons and have the potential to

reduce surgical morbidity, especially pulmonary complications, promote postoperative recovery and improve the postoperative survival rate, along with leaving only small incisions (25, 30, 31). Therefore, a minimally invasive approach may greatly improve the defects of the TA approach by eliminating its higher postoperative complications. Li KK et al. found that compared with single laparoscopic surgery, a multiple thoracoscopic operation produced little additional trauma to patients and did not increase the incidence of postoperative complications or mortality (32). However, as most of these results are retrospective studies and small in size, their conclusions should be treated with caution.

Currently, no prospective randomized controlled trials have been conducted of minimally invasive surgery for Siewert II AEG. This study will be the first multicenter randomized controlled trial focusing on Siewert II AEG treated with minimally invasive surgery, comparing the clinical efficacy of RTA versus TH. Upon successful completion of this study, we will be able to provide basic information associated with each surgical approach about disease-free survival, overall survival, postoperative complications, tumor outcomes and prognosis. The objective of this trial is to determine whether the RTA approach for Siewert II AEG patients is superior to or at least noninferior to TH in terms of surgical safety. In conclusion, the results of this study will provide clinical guidelines for choosing an approach for Siewert II AEG surgery. We hypothesized that the efficacy of digestion tract reconstruction and dissection of mediastinal lymph nodes by RTA would be better. We predict that when using minimally invasive techniques, the 3-year disease-free survival, 5-year overall survival and other prognostic indicators of RTA will be superior to or at least noninferior to that of TH, while providing a high quality of life and good postoperative outcome.

Strengths and weaknesses

Strengths

Among patients with resectable Siewert II AEG, this is the first prospective, randomized controlled trial comparing the efficacy of minimally invasive RTA and TH. Previous studies have not reported a prospective and reliable comparison of postoperative safety between the two procedures.

Limitations

The study population will be mainly composed of Chinese individuals, and its representativeness has certain limitations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Chinese Ethics Committee of Registering Clinical Trials. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ, GJ and XL developed the design and methodology. CY wrote and drafted this manuscript. ZM has made contributions to the registration of research ethics. XL and CY were responsible for developing the plans for statistical analysis. DD, PJ, RG, QY, WW, YW, HZ and XW will be responsible for the observation and data collection of those enrolled in this trial. The final manuscript will be reviewed and approved by all authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Rakesh Kapoor,
Post Graduate Institute of Medical Education and Research (PGIMER), India

REVIEWED BY
Antonella Argentiero,
National Cancer Institute Foundation (IRCCS), Italy
Zhenyu Shu,
Zhejiang Provincial People's Hospital, China
Xiongbing Zu,
Central South University, China

*CORRESPONDENCE
Wei Zhang
weizhang2000cn@163.com
Qianwen Zhang
zhangqianwen_smmu@126.com

†These authors have contributed equally to this work

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Predicting the risk of distant metastasis in patients with locally advanced rectal cancer using model based on pre-treatment T2WI-based radiomic features plus postoperative pathological stage

Chen Wang[1,2†], Jingjing Chen[3†], Nanxin Zheng[1,2†], Kuo Zheng[1,2], Lu Zhou[1,2], Qianwen Zhang[4*] and Wei Zhang[1,2*]

[1]Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China, [2]Hereditary Colorectal Cancer Center and Genetic Block Center of Familial Cancer, Changhai Hospital, Shanghai, China, [3]Graduate School of Naval Medical University, Shanghai, China, [4]Department of Radiology, Changhai Hospital, Naval Medical University, Shanghai, China

Objective: To assess the prognostic value of a model based on pre-treatment T2WI-based radiomic features and postoperative pathological staging in patients with locally advanced rectal cancer who have undergone neoadjuvant chemoradiotherapy.

Methods: Radiomic features were derived from T2WI, and a radiomic signature (RS) was established and validated for the prediction of distant metastases (DM). Subsequently, we designed and validated a nomogram model that combined the radiomic signature and postoperative pathological staging for enhanced DM prediction. Performance measures such as the concordance index (C-index) and area under the curve (AUC) were computed to assess the predictive accuracy of the models.

Results: A total of 260 patients participated in this study, of whom 197 (75.8%) were male, and the mean age was 57.2 years with a standard deviation of 11.2 years. 15 radiomic features were selected to define the radiomic signature. Patients with a high-risk radiomic signature demonstrated significantly shorter distant metastasis-free survival (DMFS) in both the development and validation cohorts. A nomogram, incorporating the radiomic signature, pathological T stage, and N stage, achieved an area under the curve (AUC) value of 0.72 (95% CI, 0.60-0.83) in the development cohort and 0.83 (95% CI, 0.73-0.92) in the validation cohort.

Conclusion: A radiomic signature derived from T2WI-based radiomic features can effectively distinguish patients with varying risks of DM. Furthermore, a nomogram integrating the radiomic signature and postoperative pathological stage proves to be a robust predictor of DMFS.

KEYWORDS

locally advanced rectal cancer, radiomics feature, nomogram, distant metastasis free survival, neoadjuvant chemoradiotherapy, radiomic feature

Introduction

Colorectal cancer ranks as the third most common cancer globally and stands as the second leading cause of cancer-related mortality worldwide (1). Rectal cancers constitute approximately 30% of all colorectal malignancies (1–3). For patients diagnosed with locally advanced rectal cancer (LARC), the current standard treatment protocol involves neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) (4, 5). Despite the significant reduction in local recurrence (LR) rates, there is not necessarily a corresponding improvement in overall survival. Distant metastasis (DM) remains the primary cause of treatment failure in LARC (4, 6). Consequently, the accurate prediction of a patient's risk of DM becomes crucial in tailoring appropriate treatments and enhancing oncological outcomes for LARC.

Similar to other malignancies, rectal cancer exhibits a tendency to metastasize to distant organs from the onset of primary lesion formation (7). This metastatic capability is closely tied to the features of the primary lesion (8). However, current practices primarily rely on histopathological examination of surgical specimens to assess the risk of distant metastasis. These pathological factors, mostly derived after nCRT, fail to evaluate the intrinsic biological heterogeneity of LARC prior to treatment, which theoretically has a close association with distant metastasis. Consequently, they fall short in providing comprehensive prognostic information about distant metastasis. Therefore, the integration of postoperative pathological factors with pre-treatment noninvasive prognostic biomarkers to assess tumor heterogeneity could be a valuable approach for facilitating personalized medicine.

Nowadays, magnetic resonance imaging (MRI) is routinely utilized for staging prior to nCRT in the treatment of LARC. This allows for an assessment of the biological heterogeneity of LARC before nCRT (9, 10). MRI-based radiomics is a non-invasive, high-throughput post-processing technique that extracts a vast number of quantitative features from standard medical images (11). Through the measurement of gray level distributions and relationships within a lesion, radiomic texture features can expose non-visual information related to tumor heterogeneity and its microenvironment. This results in a detailed and comprehensive characterization of the tumor phenotype (12).

The primary objective of this study is to investigate the relationship between pretreatment T2WI-based radiomic features and postoperative pathological staging in correlation with the risk of DM in patients with LARC. Furthermore, we aim to develop a model for personalized prediction of risk of DM, which can serve as a guide for precision medicine.

Methods

Participant inclusion

Patients with rectal adenocarcinoma treated in the department of colorectal surgery, Changhai Hospital between January 2010 and December 2018 were reviewed. The inclusion criteria were as followed: (1) LARC was determined at pre-nCRT MRI (stage pretreatment T2 weighted MR images as cT3/T4, and/or N-category positive); (2) patients received pretreatment multiparameter MRI, including high-resolution T2WI MR imaging; (3) patients were treated by long-course nCRT followed by radical TME surgical resection; (4) the LARC was the first and only malignant tumor; (5) patients received 5-fluorouracil-based adjuvant chemotherapy for 4~8 times after surgery. The exclusion criteria were as follows: (1) the quality of MR image was poor; (2) an interval longer than 16 weeks between the completion of neoadjuvant radiotherapy and surgery; (3) the followed-up time was less than 3 months.

Informed consent was obtained from each patient before nCRT and surgery. The clinicopathologic and follow-up data of all patients were collected from the prospectively maintained colorectal cancer database of Changhai Hospital, Shanghai, China. And this study was approved by the Institutional Review Board of Changhai Hospital, Secondary Military Medical University, Shanghai, China.

Neoadjuvant treatment and surgery

All patients underwent three-dimensional conformal radiation therapy (gross tumor volume, 45-50.4 Gy; clinical target volume, 1.8-2.0 Gy; a total of 25-28 fractions). Concomitantly, capecitabine (800 mg/m2 orally twice daily) was administered with radiation

therapy. After radiation therapy, patients received 5-fluorouracil-based consolidated chemotherapy for 0-3 times. TME surgery was performed with 4 to 16 weeks after the completion of radiation therapy. Afterward, patients received 5-fluorouracil-based adjuvant chemotherapy for 4-8 times.

Surgically resected specimens were evaluated by two specialist colorectal cancer pathologist, according to the Seventh American Joint Committee on Cancer (AJCC) TNM system, and the discrepancies were settled by a senior pathologist. The data about tumor staging, lymph node involvement, lymphovascular invasion (LVI), and perineural invasion (PNI) were retrospectively collected. The nCRT response was evaluated according to the 7th AJCC/NCCN tumor regression grade (TRG) scale.

Clinical endpoints and follow-up

Patients were followed up regularly after surgery by telephone contacts or interviews in outpatient clinic, with 3-month intervals for the first 2 years, then 6-month intervals for the 3rd to 5th years, and annually thereafter. The endpoint of this study was distant metastasis free survival (DMFS), which was measured from the date of surgery to the first distant metastasis, death from any cause, or the last visit in follow up (censored), and the models were built based on the DMFS. The distant metastasis was confirmed by clinical examination, imaging methods such as chest computerized tomography (CT), and abdominopelvic CT or MRI, or biopsy proven.

MRI protocol and radiomics analysis

MRI was performed with the use of a 3.0-T MRI scanner (Phillips Healthcare). Detailed information on MRI protocol was presented in Supplementary Table 1.

Each patients' MRI data were collated for tumor masking and feature extraction. The regions of interest (ROIs) were delineated manually using the itkSNAP software (www.itksnap.org). Radiomic feature extraction was performed by a panel of radiologists (Nanxin Zheng, Jingjing Chen and Chen Wang) using 3D Slicer version 4.10 (www.slicer.org), a free and open-source software, to semiautomatically segment the entire area after treatment within the rectal wall, excluding equivocal normal rectal wall and mucosal edema on the high-spatial resolution axial T2-weighted images, as shown in Figure 1.

Radiomic feature extraction and radiomic model building

The kinds of features extracted from MR image included shape, the first-order statistic, texture features (grey-level size zone matrix; grey-level co-occurrence matrix; grey-level dependence matrix; grey-level run-length matrix), and 2107 features were obtained. Only the radiomic features with good interobserver reproducibility (intraclass correlation coefficient [ICC] >0.8) were included in subsequent analyses, and 1158 features were included in the next analyses.

Univariate Cox analysis was initially used to detect the associations between each feature and the patients' DMFS. and the top 20% of the features with P< 0.15 were used for further analysis. Among those features, the Pearson correlation coefficients (r) for each feature pair were than calculated. Feature pairs with |r| >0.5 were selected, and then in each of these pairs, the feature with larger mean absolute correlation was removed. Finally, the least absolute shrinkage and selection operator (LASSO) algorithm with Cox analysis was conducted to choose the optimized subset of features to construct the final model in the development cohort, and radiomic signatures was computed.

Statistical analyses

All statistical analyses were performed by using R software (version 4.0.2, http://www.R-project.org). The differences in patient characteristics data between the training and validation cohorts were assessed by using Student t test, Man-Whitney U test, Chi-Squared tests, or Fisher exact test, where appropriate. Kaplan-Meier survival curves and the log-rank test were used to compare differences in the survival. A calibration curve was employed to calibrate the nomogram. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the model's prediction power. A two-sided P value of <0.05 was considered statistically significant.

Results

Patients' baseline characteristics

A total of 260 patients were enrolled in this study, including 197 (75.8%) men, 63 (24.2%) women. The mean age was 57.2 (11.2) years. The median follow-up period was 41.1 (IQR 27.5-54.8) months. The patients were randomly divided into a development cohort (n=156) and a validation cohort (n=104) at a ratio of 3:2. There was no significant difference between two sets in baseline demographic clinicopathological characteristics, as shown in Table 1.

Radiomic signature construction and validation

After coarse-to-fine feature selection strategy as stated in methods, 15 radiomics features were selected and then incorporated into a LASSO-Cox regression model to define the radiomic signature, as shown in Table 2. Finally, As showed in Figure 2, there was a statistically significant difference in DMFS between patients with high risk radiomic signature and those with low risk radiomic signature (P<0.001). The radiomic signature had area under the curve (AUC) values of 0.83 (95%CI 0.72 to 0.93) for 1-year DMFS and 0.72 (95%CI 0.61 to 0.82) for 3-year DMFS. In the

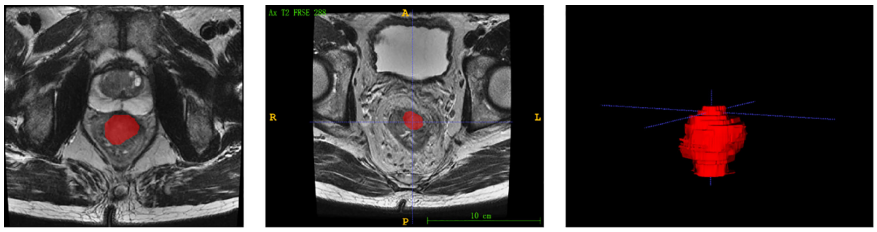

FIGURE 1
The segmentation and delineation of regions of interest (ROIs).

TABLE 1 The baseline characteristics of patients in this study.

Characteristic	Development cohort (n=156)	Validation cohort (n=104)	*P* value
Age, yrs, mean (SD)	56.5(11.4)	58.2(10.9)	0.247
Sex, female	35(22.4)	28(26.9)	0.497
BMI, kg/m^2, mean (SD)	23.3(3.3)	23.2(2.9)	0.894
Family history of maligancy, yes	13(8.3)	3(2.9)	0.376
Concomitant disease, yes	49(31.4)	30(28.8)	0.762
CEA, up	37(23.7)	24(23.1)	0.999
CA199, up	12(7.7)	7(6.7)	0.961
Gross appearance			0.999
Ulcerative	119(76.3)	80(76.9)	
Polypoid	37(23.7)	24(23.1)	
Tumor height			0.389
≥5cm	55(35.3)	43(41.3)	
<5cm	101(64.7)	61(58.7)	
pTRG			0.529
0	27(17.3)	15(14.4)	
1	37(23.7)	30(28.8)	
2	43(27.6)	33(31.7)	
3	49(31.4)	26(25.0)	
Differentiation			0.826
Disappear	27(17.3)	15(14.4)	
Well/moderately	29(18.6)	20(19.2)	
Poor	100(64.1)	69(66.3)	
Pathological T stage			0.155
0	27(17.3)	15(14.4)	
1/2	45(28.8)	42(40.4)	
3/4	84(53.8)	47(45.2)	
Pathological N stage			0.390
0	115(73.7)	79(76.0)	

(Continued)

TABLE 1 Continued

Characteristic	Development cohort (n=156)	Validation cohort (n=104)	*P* value
1	28(17.9)	13(12.5)	
2	13(8.3)	12(11.5)	
LVI[1], yes	6(3.8)	3(2.9)	0.945
PNI[2], yes	17(10.9)	12(11.5)	0.999
R0 resection, no	6(3.8)	1(1.0)	0.310
Tumor budding, yes	12(7.7)	7(6.7)	0.961
TD[3], yes	18(11.5)	16(15.4)	0.476

LVI, lymphovascular invasion.
PNI, perineural invasion.
TD, tumor deposit.

validation cohort, there was also a statistically significant difference in DMFS between patients with high risk radiomic signature and those with low risk radiomic signature (P=0.002). The radiomic signature had area under the curve (AUC) values of 0.74 (95%CI 0.55 to 0.91) for 1-year DMFS and 0.69 (95%CI 0.55 to 0.81) for 3-year DMFS.

Prognostic nomogram for DMFS

As shown in Figure 3, a pathological-radiomic nomogram combining conventional pathological T stage, pathological N stage and radiomic signature in the development cohort was built and the C-index was 0.747 (95%CI 0.711 to 0.783), higher than that of a nomogram based on conventional pathological T stage and N stage (0.696, 95%CI 0.655 to 0.737). The calibration plot for the probability of survival at 3 or 5-year after surgery showed an optimal agreement between the prediction by nomogram and actual observation. The pathological-radiomic nomogram had AUC values of 0.72 (95%CI 0.60 to 0.83) for 1-year DMFS and 0.78 (95%CI 0.68 to 0.86) for 3-year DMFS.

Validation of predictive accuracy of the nomogram for DMFS

In the validation cohort, the median follow-up time was 43.3 (IQR 34.6 to 60.7) months. The postoperative 1- and 3- DMFS rates were 86.3% (95%CI 79.8% to 93.2) and 74.7% (66.5% to 83.8%), respectively. In the validation cohort, the C-index of pathological

TABLE 2 The selected features and associated coefficients.

Features	Coefficients
original_shape_MajorAxisLength	0.68198
log_sigma_2_0_mm_3D_glrlm_RunPercentage	1.69065
log_sigma_3_0_mm_3D_glszm_GrayLevelNonUniformity	2.36652
log_sigma_4_0_mm_3D_gldm_LargeDependenceHighGrayLevelEmphasis	2.68304
log_sigma_5_0_mm_3D_firstorder_90Percentile	0.46904
wavelet_LLH_glcm_MCC	1.00224
wavelet_LHL_glcm_MCC	1.13433
wavelet_LHH_firstorder_Kurtosis	2.51254
wavelet_LHH_glszm_GrayLevelNonUniformityNormalized	1.67246
wavelet_LHH_glszm_LargeAreaLowGrayLevelEmphasis	3.19551
wavelet_LHH_glszm_SizeZoneNonUniformityNormalized	0.87635
wavelet_HLL_gldm_SmallDependenceHighGrayLevelEmphasis	3.33897
wavelet_HLH_firstorder_Skewness	0.52339
wavelet_HHL_glszm_ZoneVariance	2.04540
wavelet_LLL_gldm_LargeDependenceLowGrayLevelEmphasis	8.05213

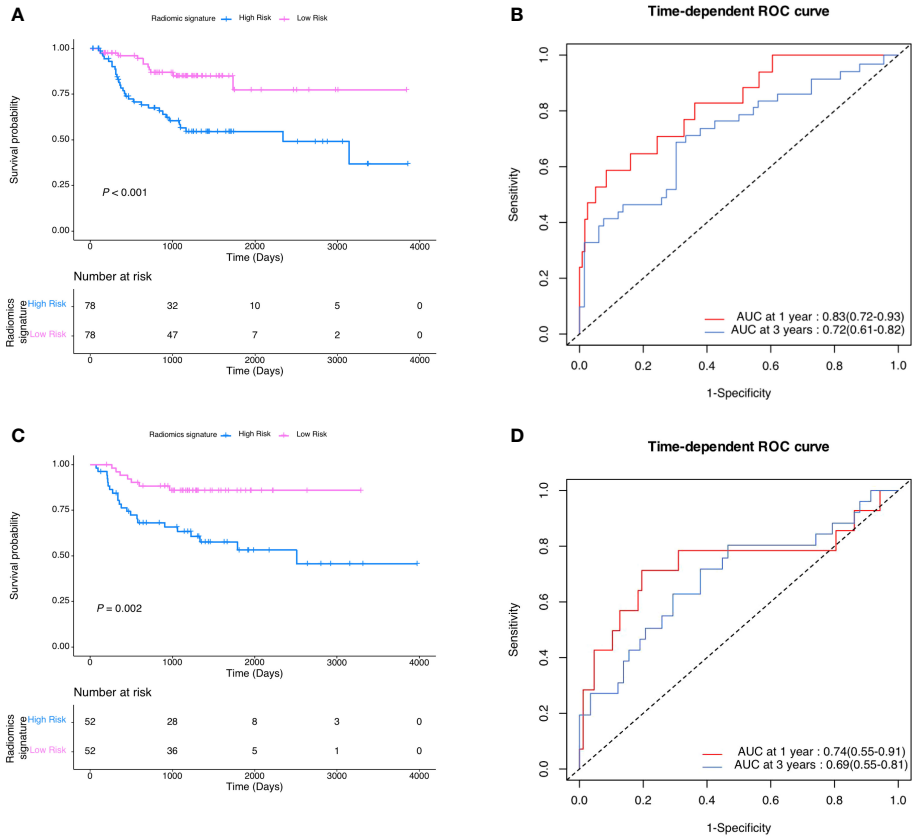

FIGURE 2
(A) DMFS according to radiomic signature in the development cohort. **(B)** Radiomic signature estimated DMFS in development cohort. **(C)** DMFS according to radiomic signature in the validation cohort. **(D)** Radiomic signature estimated DMFS in validation cohort.

radiomic nomogram for predicting DMFS was 0.788 (95%CI 0.751 to 0.825), higher than that of a nomogram based on conventional pathological T stage and N stage (0.761, 95%CI 0.720 to 0.802). As shown in Figure 4, a calibration curve showed good agreement between prediction and observation in the probability of 1-year and 3-year DMFS. The pathological-radiomic nomogram had AUC values of 0.83 (95%CI 0.73 to 0.92) for 1-year DMFS and 0.80 (95%CI 0.71 to 0.89) for 3-year DMFS.

Discussion

In this study, we constructed a prognostic index, termed a "radiomic signature," derived from T2WI radiomic features. This radiomic signature was then integrated with the conventional pathological staging system to create a pathological-radiomic nomogram for the prediction of DMFS in rectal cancer patients undergoing nCRT and surgery. The radiomic signature and the pathological-radiomic nomogram were validated in the validation cohort, demonstrating no significant statistical differences when compared to the development cohort. The results indicate that the radiomic signature offers superior prognostic discrimination. Moreover, the pathological-radiomic nomogram demonstrated superior performance over the conventional pathological staging system in predicting DMFS in both development and validation cohorts.

At present, the prognostic prediction of patients received nCRT and subsequent surgery is unsatisfactory, which partly resulted from the impact of nCRT (13). Some clinicians insisted that all locally advanced rectal cancer patients receiving nCRT were supposed to receive adjuvant chemotherapy after surgery regardless of the response towards to nCRT, due to the advanced stage of those patients at the diagnosis (14–16). Jung et al. reported a study including 551 patients concluded that adjuvant chemotherapy was significantly associated with increased DFS among patients who had undergone nCRT and surgery for LARC (17). Dossa et al. reported that the adjuvant chemotherapy even improved the overall survival of patients with rectal cancer with pCR, particularly those with pretreatment node-positive disease (18). This study implied the pretreatment clinicopathological features also were of assistance to guide of adjuvant therapy. However, a pooled analysis indicated that pCR patients would not benefit form adjuvant chemotherapy (19). The conflicting evidence of whether patients after nCRT and surgery would benefit from adjuvant therapy would result from the underestimation of detection towards tumor biology before nCRT.

In the era of precision medicine, predictive models anchored in biomarker data are becoming increasingly vital in pioneering personalized treatment plans and sophisticated therapies,

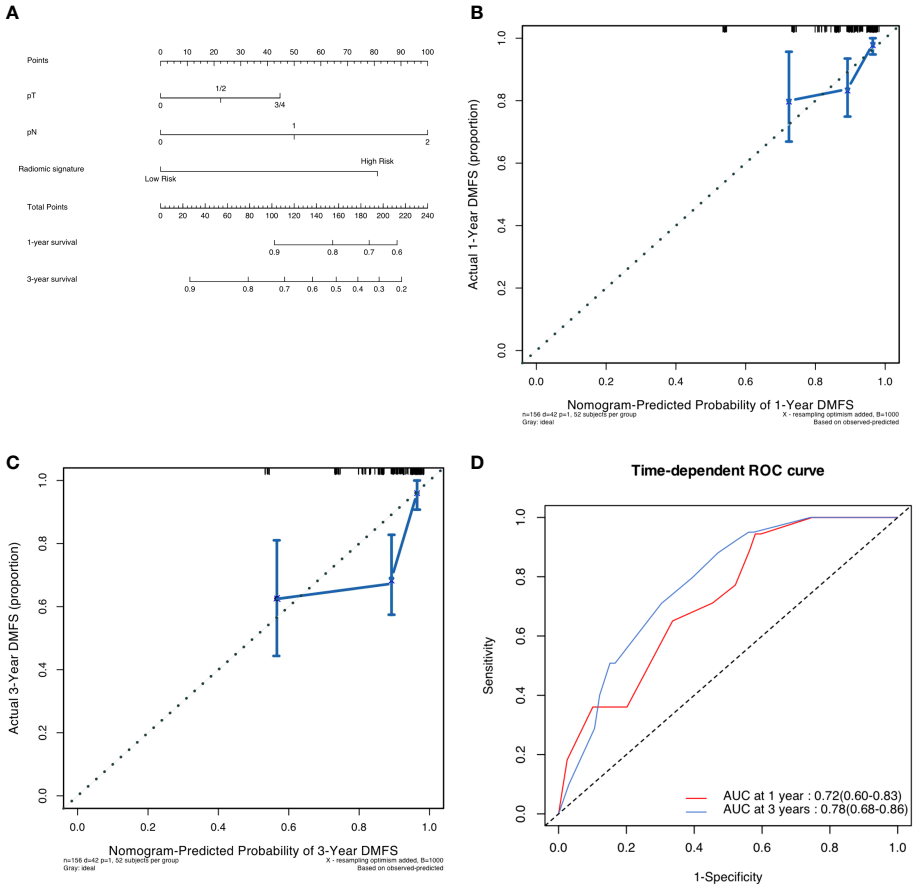

FIGURE 3
(A) Pathological-radiomic nomogram. **(B)** Calibration curve for DMFS at 1 years in the development cohort. **(C)** Calibration curve for DMFS at 3 years in the development cohort. **(D)** Time-dependent ROC curve of nomogram in development cohort.

including anti-angiogenic and immunotherapy (20, 21). However, these models frequently depend on biopsy samples that inherently offer only a limited spatial portrayal of lesions (22). This restricted sampling can potentially instigate a level of bias, occasionally resulting in false-negative diagnoses in the realm of tumor detection and characterization (23).

With the advance of theory and technique in radiology, radiomics is estimated as an effective, noninvasive method to detect the detailed and comprehensive characterization of the tumor (24). The prognostic value radiomics features has been proved in many other kinds of tumors including hepatocellular cancer, breast cancer and pancreatic cancer (24–26). In our study, T2WI-based radiomic features served as an ideal technique extracting large amounts of quantitative features from images of treatment-naive rectal cancer. After careful selection of features, radiomic signature was built to better predict the DMFS of rectal cancer patients. The pathological-radiomic nomogram also performed better than conventional pathological stage system.

The development of treatment-naive radiomic signature and pathological-radiomic nomogram has allowed for the identification of low-risk and high-risk rectal cancer patients receiving nCRT and surgery (27). To our knowledge, there is currently little use of treatment-naive radiomics combining with pathological features to predict oncologic outcomes of patients receiving nCRT and surgery. As MRI is routinely recommended before the nCRT, our study provides a new method to risk stratification for rectal patients. In addition, as MRI is routinely recommended before the nCRT, images are already widely available, the radiomic signature and pathological-radiomic nomogram could be updated conveniently and improve rectal cancer management more rapidly than other markers like molecular.

The tumor microenvironment (TME) encompasses the non-malignant cellular components within and surrounding the tumor, including but not limited to immune cells, fibroblasts, vascular structures, and the extracellular matrix. These elements collectively exert significant influence on tumor behavior and its response to therapeutic interventions. It is well-documented across various cancer types that the TME substantially impacts the propensity for distant metastases (28–30). Despite these findings, the association between the radiomic signature and the TME is yet to be fully elucidated. In our forthcoming research, we plan to investigate this relationship further, aiming to deepen our comprehension of tumor biology and potentially inform the development of innovative therapeutic strategies.

This study has several limitations. Firstly, it is a single-center study, thus the external validity of the pathological-radiomic nomogram

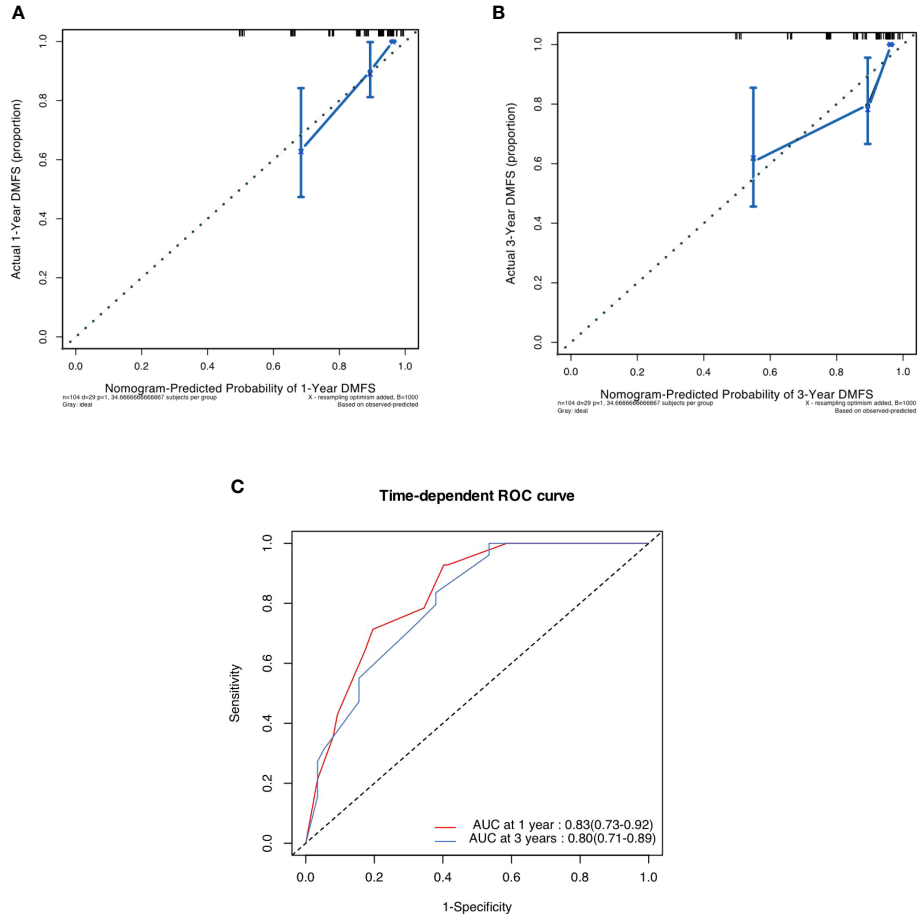

FIGURE 4
(A) Calibration curve for DMFS at 1 years in the validation cohort. **(B)** Calibration curve for DMFS at 3 years in the validation cohort. **(C)** Time-dependent ROC curve of nomogram i.

remains to be established. Future studies should incorporate data from multiple centers or leverage publicly available datasets, such as The Cancer Imaging Archive (TCIA), for further validation of our proposed nomogram. Secondly, a substantial number of radiomic features demonstrated low inter-observer agreement and were consequently excluded from our study. To mitigate this issue, we plan to enhance our workflow to minimize interobserver variability in future research. Lastly, the radiomic features for this study were derived solely from T2WI, which may not capture the full spectrum of lesion information. Subsequent studies should consider performing radiomic analysis using multiple imaging sequences to provide a more comprehensive characterization of the lesions.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The analysis data supporting the findings of this study are available from the corresponding author Wei Zhang on reasonable request. Requests to access these datasets should be directed to Wei Zhang, weizhang2000cn@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Changhai Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NZ conceived the research question, study design, supervised on methodology and technical details, and reviewed the manuscript. JC and CW contributed to the research question, study design, conducted the study, and drafted original manuscript. KZ and LZ contributed to data extraction, validation, analysis and visualization on the manuscript. WZ and QZ provided critical consultation and interpretation from clinical perspective and contributed to manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1109588/full#supplementary-material

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