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Recurrence of liver tumors: The issue of iterative approaches

Edited by
Umberto Cillo, Alessandro Vitale and Alessandra Bertacco

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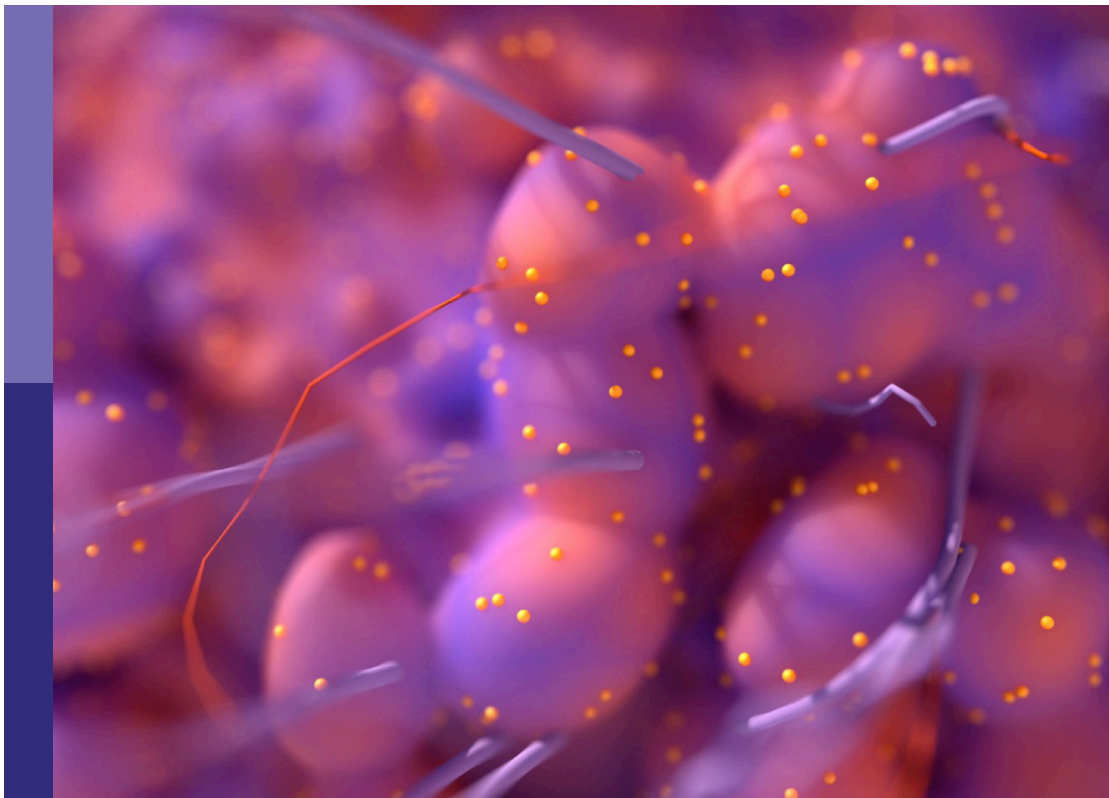

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Recurrence of liver tumors: The issue of iterative approaches

Topic editors

Umberto Cillo — University of Padua, Italy

Alessandro Vitale — University Hospital of Padua, Italy

Alessandra Bertacco — Padua University Hospital, Italy

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EDITED AND REVIEWED BY
Francesco Giovinazzo,
Agostino Gemelli University Polyclinic (IRCCS), Italy

*CORRESPONDENCE
Michele Finotti
mi6le@libero.it

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Editorial: Recurrence of liver tumors: the issue of iterative approaches

Michele Finotti[1,2]*, Alessandra Bertacco[3], Francesco Enrico D'amico[3], Alessandro Vitale[3], Enrico Gringeri[3] and Umberto Cillo[3]

[1]Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, TX, United States, [2]4th Surgery Unit, Regional Hospital Treviso, Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche (DiSCOG), University of Padua, Padua, Italy, [3]Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche (DiSCOG), General Surgery 2-Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Padua, Padua, Italy

KEYWORDS

hepatocellular carcinoma, colorectal liver metastases (CLM), cholangiocarcinoma, liver transplant (LT), iterative approach

Editorial on the Research Topic
Recurrence of liver tumors: the issue of iterative approaches

Primary and secondary liver tumors are mainly treated with a multimodal treatment (chemotherapy and liver surgery) aiming for the best long-term patient Overall Survival (OS). However, Liver Tumor Recurrence (LTR) is frequent, and in this context, multiple tools are now available: liver resection with parenchyma sparring techniques, mini-invasive approaches, and multiple and multimodal surgical and medical therapies, based on the liver tumor's features.

In this Frontiers issue, "*Recurrence of Liver Tumors: The Issue of Iterative Approaches*", we analyzed the role of surgery on the LTR treatment, through 16 peer-reviewed open-access publications including 173 authors and experts in the field from 8 different countries, 2 study groups, European Hepatocellular Cancer Liver Transplant (EurHeCaLT) and Italian Liver Cancer (ITA.LI.CA) group and 39 reviewers and co-editors.

The first set of papers is dedicated to hepatocellular carcinoma (HCC), the most common primary liver cancer and the second most common cause of cancer-related death worldwide. HCC is mostly associated with cirrhosis/end-stage liver disease and, compared to other liver tumors, the prognosis is linked not only to the tumor features but also to the stage of the underlying liver disease.

Liver transplant (LT) is the best therapeutic option but, mostly due to organ shortage, is not always feasible.

In this setting, the iterative approach is the natural consequence of the HCC history after any type of treatment: the intrahepatic recurrence. Even with first-line treatments, LT, and curative hepatectomy, intrahepatic recurrence is common, as shown by Lai et al.

If HCC recurrence is expected, indications, timing, and type of treatment according to the patient's stratification by the risk of recurrence (personalized medicine) are still a matter of debate.

In the first series of articles, we acknowledge that different therapeutic options are accessible (repeat LR, ablation techniques, TACE) in a setting of iterative treatment and we discussed the lacking of high evidence-based studies on the management of recurrent HCC.

The mini-invasive approach is the key to iterative treatment for RLT, especially in HCC. The advantages, compared to open surgery, are fewer intra and postoperative complications, faster postoperative recovery, and possible repetition of the treatment in a shorter time.

Chen et al. evaluated the role of curative liver resection for recurrent HCC with a mini-invasive approach compared to open resection with a propensity score–based study and confirmed by an up-to-date meta-analysis.

The study showed that laparoscopic liver resection is associated with lower blood loss, better post-operative liver function, and shorter post-operative course with comparable operative time, complication, and mortality rate confirmed also by Hao et al.

Thanks to the improvement of laparoscopic surgical techniques, the study showed that the mini-invasive approach can be safely applied also in challenging tumors, such as recurrent HCC located in posterosuperior segments or with a maximum size of >5 cm. The authors showed also an interesting relationship between lower post-operative inflammation-based markers and enhanced recovery in the population treated with the mini-invasive approach.

Mini invasiveness and fast recovery are not the only essential element for the iterative process, but also sparing as much as liver possible for possible future treatments, particularly in patients with liver cirrhosis and/or multiple nodules/portal hypertension.

Cheng et al. addressed this issue, showing that liver resection with very narrow surgical margins (<1mm) has outcomes comparable to those with wider margins.

These initial results seem promising, but long-term oncologic outcomes and future randomized trials are needed. Furthermore, the role of the robotic approach in the iterative treatment of HCC recurrence is an ongoing topic that has to be addressed and evaluated as well.

As shown, liver resection is the first line treatment of HCC recurrence when LT is not indicated/possible. However, repeat hepatectomy is not always feasible, due to liver function, number/size of HCC recurrence, and/or patient performance status.

Recent studies showed that Trans Arterial ChemoEmbolization (TACE) is a possible but, if applied alone, limited alternative in terms of efficacy.

Pelizzaro et al. showed that TACE can be an important iterative tool for an upward shift toward curative therapies that provide higher survival benefits compared to TACE repetition (LR, LT, and ablation).

Also, Zheng et al. showed that TACE in combination with radiofrequency ablation (RFA) (TACE-RFA) has similar outcomes compared to repeat hepatectomy in the treatment of recurrent HCC in terms of safety, overall survival, and progression-free survival. To note, for the first time the study showed similar results for HCC diameter > 5cm and lower post-operative complications compared to repeated liver resection. Considering the low impact TACE-RFA has on the postoperative course of the patient, this tool can be considered as a possible alternative to liver resection and/or as a bridge to LT. Further studies are mandatory.

In the second series, we proposed studies evaluating the impact of HCC recurrence after LT.

In a large European cohort, Lai et al. confirmed LT as the best therapeutic option for HCC with the excellent long-term outcome at 5 and 10 years, despite the recent widened of HCC selection criteria outside Milan criteria.

The study pointed out that HCC recurrence can happen >5 years after LT, especially in patients with previous multimodal iterative treatment, as described by Pagano et al. Adequate post-LT surveillance and further iterative treatment even after LT has to be considered.

Therefore, in the case of HCC recurrence, multiple therapeutic options can be offered in different possible combinations and timing (re-resection + TACE, TACE + RFA, re-resection + RFA, etc.), underlining the importance of a mini-invasive approach and liver sparing to enhance faster recover and reduce the impact on liver dysfunction.

However, there is still debate about the timing and type of tool to offer and which population would benefit the most.

We addressed this issue in the third series of articles, proposing evidence-based tools to predict accurately the pre- and post-operative HCC recurrence and to guide the most beneficial pharmacological or surgical treatment/monitoring for that specific patient (personalized medicine).

Different staging systems can be used to clinically stage and guide the HCC treatment, such as the American Joint Commission on Cancer (AJCC), the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP) system, the albumin-bilirubin (ALBI) grading system. However, they are not designed to guide physicians on the treatment of recurrent HCC, and one of the limitations of the current known risk features for early recurrence is that most of them are based on postoperative histopathological tissue.

Recently, the China liver cancer (CNLC), an evidence-based staging system, gained interest thanks to its ability to perform globally better than other systems, especially compared to BCLC. Liao et al. proposed two nomograms to implement the CNLC for recurrent HCC with three independent risk factors for OS (cirrhosis, GGT, and tumor differentiation) and one for RFS (AFP). This resulted in a better ability to predict survival and HCC recurrence in patients treated with curative hepatectomy, helping the physician to identify a high-risk population with potential early recurrence.

With the same goal, He et al. proposed to use of multimodal (MRI/CT) radiomics models to predict HCC prognosis and recurrence before treatment, and Chen et al. proposed two nomograms incorporating the most important predictive factor for recurrence and OS (microvascular invasion).

Knowing a specific population with a higher risk of recurrence can help to guide toward a more aggressive or iterative treatment (i.e. LR + TACE, LR + RFA).

Furthermore, Zou et al. proposed a novel blood index signature (BIS) able to accurately predict HBV-associated HCC (HBV-HCC) recurrence after curative hepatectomy. Based on the risk of HCC recurrence, the study identified a high-risk group that benefits specifically from adjuvant TACE.

In the second set of papers, we translated the same concept of iterative surgery to all the tumors with a high risk of recurrence after primary treatment, such as ColoRectal Liver Metastases (CRLM) and cholangiocarcinoma (CCA), concepts summarized by Aquina et al. and Bekki et al. in their comprehensive literature reviews.

As well HCC, CRLM, and CCA face the issue of a lack of patient stratification and an accurate prognostic model able to predict the recurrence and guide the application of an iterative approach. Jin et al. faced the issue of patient stratification in recurrent CRLM proposing a nomogram based on age, TN stage, neoadjuvant chemotherapy, and primary tumor position to identify optimal patients that may benefit the most from an iterative treatment.

On the same line, Liu et al. developed a prognostic model with good calibration for risk estimation of CCA recurrence.

Liver resection is the treatment of choice, but ablation techniques are often applied as iterative CRLMs treatment, thanks to the mini-invasive approach (percutaneous or video-assisted) and liver tissue sparing. Guadagni et al. showed that for CRLMs <4cm, liver microwave ablation has mid-term oncological outcomes similar to liver resection. In case of multiple lesions, and recurrent and deep liver segments, ablation can be an effective alternative to resection to improve liver sparing and expedite the post-operative course, given possible future further treatments.

In conclusion, in tumors with a high risk of recurrence, the iterative approach is essential to improve the patient's OS and keep the liver disease under control. Multiple therapeutic sessions with different tools are often required to achieve a complete liver tumor regression and radicality. Keys elements for the iterative approach are mini-invasiveness, low post-operative patient impact, fast recovery, and repeatable over time.

The series pointed out that the decision of the therapeutic options should be tailored to that specific patient (personalized medicine) based on the type of liver cancer and the patient's features. The efficacy of that specific surgical tool (resection, ablation, TACE, etc.) is not merely related to the technique itself but it is mainly associated with the correct patient selection that will benefit the most from that specific procedure. Further studies evaluating the best sequence and timing of the iterative surgery, and implementing the current staging system are necessary to achieve the personalized medicine concept.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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Laparoscopic vs. Open Repeat Hepatectomy for Recurrent Liver Tumors: A Propensity Score–Matched Study and Meta-Analysis

Jia-Feng Chen[1†], Xiu-Tao Fu[1†], Zheng Gao[1†], Ying-Hong Shi[1], Zheng Tang[1], Wei-Ren Liu[1], Xin Zhang[1], Qiang Gao[1], Guang-Yu Ding[1], Kang Song[1], Xiao-Ying Wang[1], Jian Zhou[1,2], Jia Fan[1,2]* and Zhen-Bin Ding[1]**

[1] Department of Liver Surgery & Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China, [2] Key Laboratory for Carcinogenesis and Cancer Invasion, Chinese Ministry of Education, Shanghai, China

Background: It remains unclear whether the short-term benefits of laparoscopic repeat hepatectomy (LRH) accrue to patients with recurrent liver tumors. The present study aimed to report our own center's experience and perform a meta-analysis to evaluate the safety and feasibility of LRH in comparison with open repeat hepatectomy (ORH) for treating recurrent liver tumors.

Patients and Methods: A propensity score–matched study was performed including 426 patients receiving LRH or ORH for recurrent hepatocellular carcinoma between January 2017 and December 2018. Surgical outcomes and perioperative inflammation-based markers, including monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune–inflammation index were collected from medical records and analyzed. Additionally, a systematic literature review was performed to identify relevant studies in PubMed, EMBASE, Web of Science, and Cochrane library databases up to October 1, 2020. Information including patient demographics, pathologic characteristics, and short-term outcomes was extracted and analyzed using random- or fixed-effects models.

Results: Of 68 LRHs, 57 were matched with an ORH finally. Our study demonstrated that LRH was significantly associated with less intraoperative blood loss (50 vs. 100 mL; $P < 0.001$), lower rate of hepatic inflow occlusion (10.52 vs. 33.3%; $P = 0.003$), and shorter postoperative hospital stay (5 vs. 6 days; $P = 0.001$) after 1:1 propensity score matching. The operation time, rate of blood transfusion, and postoperative complications were similar between the two groups. Moreover, all four inflammation-based markers were significantly lower in LRH group on postoperative day 1. In the meta-analysis, a total of 12 studies comprising 1,315 patients receiving repeat hepatectomy met the selection criteria. Similar to our own study, the meta-analysis showed shorter hospital stay [standard mean difference (SMD) = −0.51, 95% confidence interval (CI) = −0.79 to −0.22, $P < 0.001$], less intraoperative blood loss (SMD = −0.79, 95%

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Alessandro Vitale,
University Hospital of Padua, Italy

Reviewed by:
Paul Willemsen,
Hospital Network Antwerp (ZNA), Belgium
Alfonso Recordare,
Ospedale dell'Angelo, Italy
Fabio Melandro,
Pisana University Hospital, Italy

***Correspondence:**
Zhen-Bin Ding
ding.zhenbin@zs-hospital.sh.cn
Jia Fan
fan.jia@zs-hospital.sh.cn
Xiao-Ying Wang
wang.xiaoying1@zs-hospital.sh.cn

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

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CI = −1.11 to −0.47, $P < 0.001$), and lower rate of major postoperative complications [odds ratio (OR) = 0.35, 95% CI = 0.19–0.66, $P = 0.001$] in the LRH group. There was no difference in the field of overall postoperative complication and operation time between LRH and ORH groups.

Conclusion: Compared with ORH, LRH results in relatively better surgical outcomes and faster postoperative recovery. It could be considered a feasible and effective option for the treatment of recurrent liver tumors.

Keywords: recurrent liver tumors, repeat hepatectomy, laparoscopic surgery, open surgery, meta-analysis

INTRODUCTION

Liver tumor is one of the most common malignant tumors and ranks as the fourth leading cause of cancer-related mortality (1). Hepatocellular carcinoma (HCC) is the most common pathological type of liver tumors, especially in the Asia Pacific region (2). Although liver cancer can be treated by curative hepatectomy with other various approaches, the recurrence rate after primary hepatectomy remains high (3). As for the intrahepatic recurrence, the repeat hepatectomy is still considered to be one of the most important potential curative therapies.

A history of abdominal surgery was once considered a contraindication to laparoscopic operation. However, with the advancement and widespread usage of laparoscopic technique and instruments in recent decades, laparoscopic hepatectomy (LH) has been gaining popularity as an alternative to open hepatectomy. In addition, LH for liver tumors, especially for HCC, has been shown to achieve superior short-term outcomes and equivalent oncological prognosis (4). Besides the inherent movement restrictions and disorientation, adhesion and deformity of the liver caused by previous operation disrupt the liver mobilization and make the identification of important vessels and Glissonian pedicles more difficult. Therefore, patients receiving laparoscopic repeat hepatectomy (LRH) suffer from increasing rates of conversion and postoperative complications (5). It is unclear whether or not patients with recurrent liver tumors benefit from LRH.

Enhanced Recovery After Surgery program is a multimodal perioperative care protocol to accelerate recovery by minimizing the physiologic stress of operations (6). The physiologic stress has been linked to changes of organ functions, which could be reflected by inflammation-based markers. The advantage of LRH in recurrent HCC (rHCC) patients has not been fully elucidated, especially for the relationship between postoperative inflammation and short-term outcomes. Therefore, we explored changes of inflammation-based markers after surgery. Moreover, with the same discharge criteria, hospital stay seems to be an important indicator in evaluation of physical rehabilitation. The factors that affect discharge are complex, including body temperature, liver function, pain, diet, patient choice, and so on. The inflammatory response markers can truly reflect the stress state of the patient, and its recovery is an important aspect of physical rehabilitation. Therefore, we also invested the relationship between inflammation-based markers and hospital stay.

To the best of our knowledge, no randomized controlled trials (RCTs) and even limited retrospective studies have been performed to compare the outcomes between LRH and open repeat hepatectomy (ORH). Although a few systematic reviews have been conducted to assess safety and efficiency of LRH for recurrent liver tumors, some high-quality multicenter studies have been published recently and not included in these reviews (7, 8). Herein, the purpose of this study was to carry out a propensity score–based study and a meta-analysis to compare the postoperative outcomes of patients who underwent LRH with those of patients receiving ORH and produce recommendations on the safe and effective practice for recurrent liver tumors.

MATERIALS AND METHODS

The Propensity Score–Matched Study

From January 2017 to December 2018, 729 consecutive patients received curative hepatectomy for recurrent liver tumors at Liver Cancer Institute, Zhongshan Hospital, Shanghai, China. Patients were excluded if they underwent a two-stage procedure, radiofrequency ablation, or other additional operations simultaneously in this study. Of these, 426 patients diagnosed with rHCC pathologically were included in the analysis. The indications for LRH consisted of the following: (1) Child–Pugh grade A or B liver function that recovered to grade A after liver-protective treatment, (2) no clinical signs of major vessel or extrahepatic organs invaded by tumors, (3) absence of gross ascites or severe complications after the previous operation, and (4) no other noteworthy surgical contraindications. The indications for ORH were similar to those for laparoscopic surgery. The final choice of surgical approach was depended on surgeon's preference and experience. The Ethics Committee of Zhongshan Hospital approved the study design (no. B2020-363), and written informed consent was obtained from each patient.

The surgical procedure and surveillance after repeat hepatectomy were similar with those of primary hepatectomy that we described previously (9). All operations were performed by two experienced hepatobiliary surgeons.

Data Collection

The data collected included baseline, perioperative, and pathologic characteristics from medical records. The following

baseline characteristics were obtained: patient demographics, history of previous hepatectomy, the Child–Pugh classification, and preoperative liver function [hepatitis B virus (HBV) infection status, presence of liver cirrhosis]. The approach to previous operation was considered open when patients had received both open hepatectomy and LH previously.

Perioperative characteristics investigated were as follows: conversion rate, duration of surgery, blood transfusion rate, Pringle maneuver requirements, intraoperative blood loss, postoperative morbidity, 90-day mortality, and duration of hospital stay. Postoperative morbidity was classified according to the Clavien–Dindo classification system (10), and the morbidity with grade II or above was recorded in our analysis. Pathologic characteristics consisted of number of tumors, size of maximum tumor, encapsulation of tumors, and location of tumors. Anterolateral hepatectomy was defined as a resection of tumors from segments II, III, IVb, V, or VI, otherwise regarded as posterosuperior hepatectomy.

In addition, we recorded total bilirubin (TB), aspartate transaminase (AST), alanine transaminase (ALT), and prothrombin time (PT) from liver function tests, and lymphocyte, neutrophil, monocyte, and platelet counts from hematological blood tests carried out on preoperative day and postoperative day (POD) 1 and POD 3. The systemic immune–inflammation index (SII) was measured as platelet count × neutrophil count/lymphocyte count, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) were also calculated and compared between the two groups.

Statistical Analysis

Continuous variables were presented as median (range) or mean ± standard deviation (SD), as appropriate for the data distribution. Continuous variables were compared using Mann–Whitney *U*-test (Wilcoxon rank sum test) or Student's *t*-test. Categorical variables were compared using Pearson χ^2 test or Fisher's exact test, as appropriate. To minimize the influence of potential selection bias, a 1:1 propensity score matching (PSM) was used based on the following eight factors: age, gender, tumor number, maximum tumor size, tumor location, liver cirrhosis, previous hepatectomy approach, and HBV infection status. The choice of these factors was based on their value in the decision to proceed with LRH or ORH and their influence on surgical outcomes. The PSM was performed using nearest neighbor matching with a caliper width of 0.02 according to the recommendations of Lonjon and colleagues (11). X-tile software version 3.6.1 was used to determine the best cutoff values of four inflammation-based markers. The Kaplan–Meier method was used to calculate the hospitalization rate. The log-rank test was used to compare the significance of hospitalization rate between groups. Cases in the LRH group that were converted to ORH were analyzed in the LRH group according to intention-to-treat principles. Two-tailed $P < 0.05$ was considered to be statistically significant. All analyses were performed using SPSS version 25.0, R software version 4.0.2, and GraphPad Prism 8.

SYSTEMATIC REVIEW AND META-ANALYSIS

Search Strategy and Selection Criteria

A comprehensive and systematic review search in PubMed, EMBASE, Web of Science, and Cochrane Library databases was performed by two researchers (Jiafeng Chen and Xiutao Fu) independently to retrieve all relevant studies published up to October 1, 2020. The MeSH term and synonyms were as follows: "recurrent liver cancer," "repeat," "open hepatectomy," and "laparoscopic hepatectomy." The references of eligible studies were also reviewed to identify potential relevant articles. The study was registered with the PROSPERO register of systematic review (registration no. CRD 42020219438) and was conducted according to the search strategy based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (12).

Initially, the titles and abstracts of all extracted records were screened by two researchers (Jiafeng Chen and Xiutao Fu) to exclude review articles, letters, editorials, case reports, and other irrelevant studies. Then, the studies deemed potentially eligible were full-text assessed. All included studies in this meta-analysis satisfy the following criteria. The inclusion criteria were as follows: (1) patients were diagnosed with recurrent liver tumors; (2) patients had been treated by LRH or ORH; and (3) data available on the key surgical outcomes in the two respective groups. The exclusion criteria were as follows: (1) records reported in non-English languages; (2) records did not report complete and clear data of surgical outcomes; and (3) records did not fulfill the above inclusion criteria. The discrepancies were resolved by discussion with a third author (Zheng Gao).

Data Extraction and Quality Assessment

Data were extracted by two reviewers (Jiafeng Chen and Xiutao Fu) independently from the studies as follows: the first author, year of publication, number of patients, and patients' baseline characteristics. Intraoperative characteristics (e.g., operation time, blood loss, blood transfusion rate, use of Pringle maneuver), short-term outcomes, and pathologic characteristics were also recorded. The quality of included studies was evaluated using the Newcastle–Ottawa Quality Assessment Scale (NOS), which contains selection, outcome, and comparability assessment. A minimum of six scores was identified as high-quality study.

Statistical Analysis

Odds ratio (OR) with 95% confidence interval (CI) was used for analysis of dichotomous variables, and standard mean difference (SMD) with 95% CI was calculated for continuous data. If means and SDs were not provided, they were imputed from medians and ranges by the method of Hozo et al. (13). The heterogeneity was assessed by the I^2 statistics and Cochran's Q test. When $I^2 > 50\%$ and $P < 0.1$, a random-effects model was used. Otherwise, a fixed-effect model was applied. With respect to publication bias, it was assessed by observing asymmetry of funnel plots, which was further evaluated by Egger's and Begg's test. Statistical significance was denoted by $P < 0.05$ except where indicated. All

TABLE 1 | Patient baseline characteristics and tumor characteristic.

Characteristic	Before PSM			After PSM		
	LRH ($n = 68$)	ORH ($n = 358$)	*P*-value	LRH ($n = 57$)	ORH ($n = 57$)	*P*-value
Age (years)	56.0 (36.0–78.0)	60.0 (27.0–86.0)	0.099†	56.0 (36.0–78.0)	59.0 (34.0–77.0)	0.910†
Gender (male/female)	54/14	320/38	0.021*	49/8	50/7	0.782*
Maximum tumor size (cm)	1.5 (0.6–10.0)	2.0 (0.5–13.0)	<0.001†	1.5 (0.6–4.5)	1.7 (0.8–4.5)	0.433†
No. of tumors	1.0 (1.0–4.0)	1.0 (1.0–6.0)	0.051†	1.0 (1.0–4.0)	1.0 (1.0–2.0)	0.487†
Previous surgical approach						
Laparoscopic	16	21	<0.001*	7	5	0.542*
Open	52	337		50	52	
No. of previous surgery	1.0 (1.0–2.0)	1.0 (1.0–5.0)	0.408†	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.182†
Tumor location						
Anterolateral	53	179	<0.001*	43	47	0.358*
Posterosuperior	15	179		14	10	
HBV (Y/N)	63/5	325/33	0.621*	52/5	53/4	1.0*
Child–Pugh grade (A/B)	68/0	357/1	1.0*	57/0	57/0	1.0*
Liver cirrhosis (Y/N)	35/33	180/178	0.857*	31/26	31/26	1.0*
TB (μmol/L)	11.35 (2.7–37.7)	13.0 (3.1–37.5)	0.120†	11.2 (2.7–37.7)	13.2 (4.7–36.4)	0.134†
ALT (U/L)	20.5 (6.0–49.0)	21.0 (5.0–219.0)	0.474†	20.0 (6.0–43.0)	21.0 (8.0–86.0)	0.512†
Albumin (g/L)	45.0 (30.0–53.0)	44.0 (26.0–69.0)	0.742†	45.0 (30.0–53.0)	46.0 (36.0–69.0)	0.345†
PT (s)	11.6 (10.0–14.0)	11.5 (9.6–15.3)	0.752†	11.5 (10.0–14.0)	11.5 (10.2–13.7)	0.986†
AFP (ng/mL)						
<20	41	236	0.500*	36	36	0.188*
20–400	17	84		12	16	
≥400	8	28		7	2	
Tumor capsule						
None and partial	42	202	0.414*	33	29	0.452*
Complete	26	156		24	28	

Values are median (range).

**Pearson χ^2 tests or Fisher's exact test, as appropriate.*

† Mann–Whitney U-test (Wilcoxon rank sum W-test).

PSM, propensity score matching analysis; LRH, laparoscopic repeat hepatectomy; ORH, open repeat hepatectomy; HBV, hepatitis B virus; TB, total bilirubin; ALT, alanine transaminase; PT, prothrombin time; AFP, α-fetoprotein; Y, yes; N, no.

P-values were two-tailed. All analyses were performed using R software version 4.0.2 and Review Manager version 5.3.

RESULTS

Results of Our Retrospective Study

Patients' Characteristics

A total of 426 patients underwent repeat hepatectomy for rHCC, 68 treated by LRH and 358 treated by ORH. In the LRH group, six patients required conversion from laparoscopic to open surgery. Of these, three patients had dense intra-abdominal adhesions or the development of portal hypertension and collateral circulation, which may increase the risks of uncontrolled bleeding, injury to important hepatic vessels, biliary trees, and adjacent organs. Another reason of conversion in two patients is failure to localize tumors because of distinct changes of anatomical landmarks. In addition, one patient had conversion to open hepatectomy because of difficulty of dissecting hepatic hilar region. The baseline and pathologic characteristics of the LRH and ORH groups are summarized in **Table 1**. The ORH group had a larger size of maximum tumor (2 vs. 1.5 cm; $P < 0.001$) and higher rates of posterosuperior resection (50.0 vs. 22.1%; $P < 0.001$). The proportion of previous LH in the LRH group was higher than that in the ORH group (23.5 vs. 5.9%; $P < 0.001$). Owing to the application of 1:1 PSM, 114 patients were selected for comparison, and details of PSM are shown in the dot plot and jitter plot (**Figure 1**). Baseline characteristics and tumor characteristics were well-balanced between the two groups, with no significant difference (**Table 1**). In addition, all patients included had ever hepatectomy once or more with liver cirrhosis (stage 4 fibrosis) observed in 62 patients (54.4%). Given these facts, most of our patients underwent partial liver resection in order to reserve enough liver function, while ensuring enough margin (>1 cm). Except for partial resection, five patients received anatomical resection (segmentectomy) in the LRH group and eight in the ORH group (8.7 vs. 14%; $P = 0.377$). In other words, there also was no significant difference in the type of liver resection.

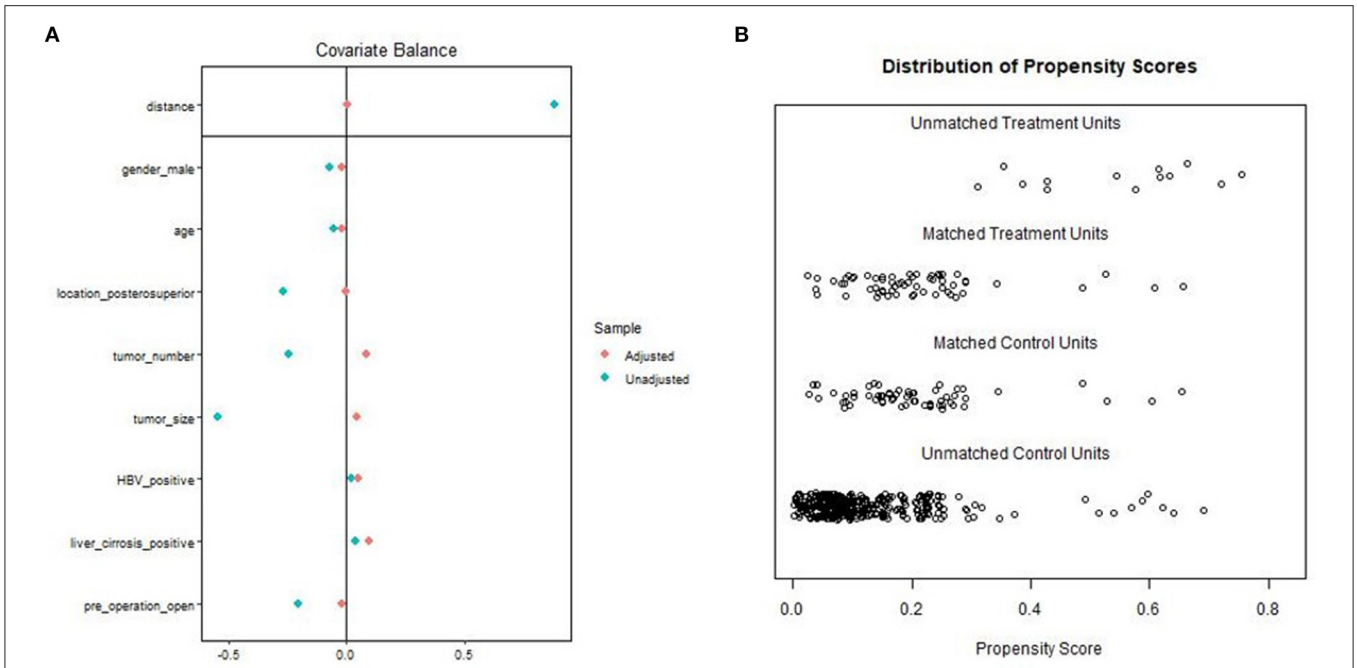

FIGURE 1 | Propensity score matching: **(A)** Dot plot of the standardized mean difference (SMD). **(B)** Propensity score matching jitter plot.

TABLE 2 | Surgical outcomes after PSM.

Outcomes	LRH ($n = 57$)	ORH ($n = 57$)	*P*-value
Conversion	6 (10.5%)	NA	NA
Operation time (min)	131.0 (45.0–415.0)	124.0 (57.0–264.0)	0.285†
Blood loss (mL)	50.0 (10.0–600.0)	100.0 (20.0–800.0)	<0.001†
Transfusion (yes/no)	1/56	0/57	1.0*
Pringle maneuver (yes/no)	6/51	19/38	0.003*
Complication (yes/no)	1/56	2/55	1.0*
AST (U/L)	103.0 (34.0–2,209.0)	214.0 (77.0–1,916.0)	<0.001†
ALT (U/L)	104.0 (19.0–1,828.0)	187.0 (51.0–1,804.0)	<0.001†
TB (μmol/L)	25.6 (12.6–75.7)	28.3 (15.2–62.4)	0.069†
PT (s)	12.9 (11.1–17.3)	13.7 (11.5–17.2)	<0.001†
Hospital stay (days)	5.0 (3.0–13.0)	6.0 (4.0–33.0)	0.001†

Values are median (range).
**Pearson χ^2 tests or Fisher's exact test, as appropriate.*
† Mann–Whitney U-test (Wilcoxon rank sum W-test).
LRH, laparoscopic repeat hepatectomy; ORH, open repeat hepatectomy; AST, aspartate transaminase; ALT, alanine transaminase; TB, total bilirubin; PT, prothrombin time.

Comparison of Surgical Outcomes Between LRH and ORH for rHCC

Propensity score–adjusted analyses demonstrated that the median blood loss was significantly lower in the LRH group (50 mL; range = 10–600 mL) than ORH group (100 mL; range = 20–800 mL) ($P < 0.001$). In addition, LRH was associated with less appliance of Pringle maneuver (10.5 vs. 33.3%; $P = 0.003$) and shorter postoperative hospital stay (5 vs. 6 days; $P = 0.001$). The median operation time was similar in the LRH group (131 min; range = 45–415 min) and ORH group (124 min; range = 57–264 min) ($P = 0.285$). With respect to postoperative complications, one patient in LRH group and two in the ORH group developed complications of grade II or above. All three patients experienced pleural effusion requiring drainage, and one patient in the ORH group experienced peritoneal effusion simultaneously. No postoperative mortality occurred in either group (**Table 2**).

The levels of ALT, AST, TB, and PT, especially on the peak day, were lower in the LRH group than those in the ORH group ($P < 0.001$, $P < 0.001$, $P = 0.069$, and $P < 0.001$, respectively) (**Table 2**). In addition, the mean values of SII, NLR, PLR, and MLR on POD 1 and POD 3 are summarized in **Figure 2**. The four inflammation-based markers were comparable in the two groups before surgery. As compared with those of LRH group, SII, NLR, PLR, and MLR in the ORH group were significantly higher on POD 1 [1,929.7 ± 1,017.3 vs. 1,490.0 ± 797.0 ($P < 0.001$); 14.1 ± 8.0 vs. 10.1 ± 4.3 ($P < 0.001$); 169.1 ± 71.9 vs. 148.6 ± 60.0 ($P = 0.037$); 1.11 ± 0.51 vs. 0.88 ± 0.30 ($P = 0.001$), respectively]. Although all these four markers were elevated in the ORH group on POD 3, only NLR and MLR were significantly higher than those in the LRH group [8.5 ± 5.8 vs. 5.3 ± 2.9 ($P < 0.001$); 0.94 ± 0.40 vs. 0.73 ± 0.32 ($P = 0.003$)]. We also invested the relationship between inflammation-based markers and hospital stay by performing a quantitative X-tile software analysis. The optimal value was produced when applying 431.7 of SII on POD 3 as cutoff value to divide the cohort into two subsets (**Figures 3A,B**). The Kaplan–Meier plot showed that SII ≤ 431.7 on POD 3 was associated with shorter hospital stay ($P < 0.001$) (**Figure 3C**). These results provide evidence that LRH was associated with faster postoperative recovery.

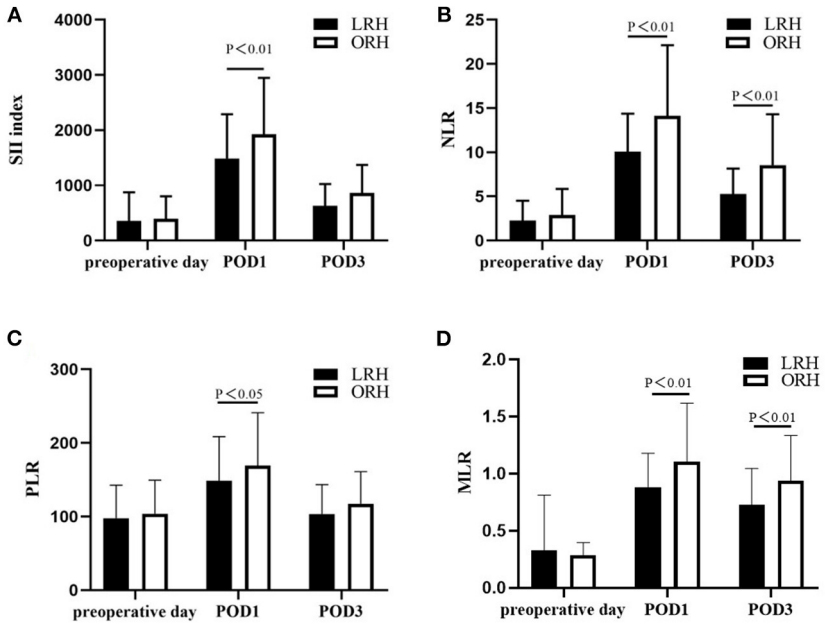

FIGURE 2 | Changes in the level of **(A)** SII, **(B)** NLR, **(C)** PLR, and **(D)** MLR on preoperative day, postoperative day (POD) 1 and POD 3. Values are presented as mean ± standard deviation. SII, systemic immune–inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelets-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

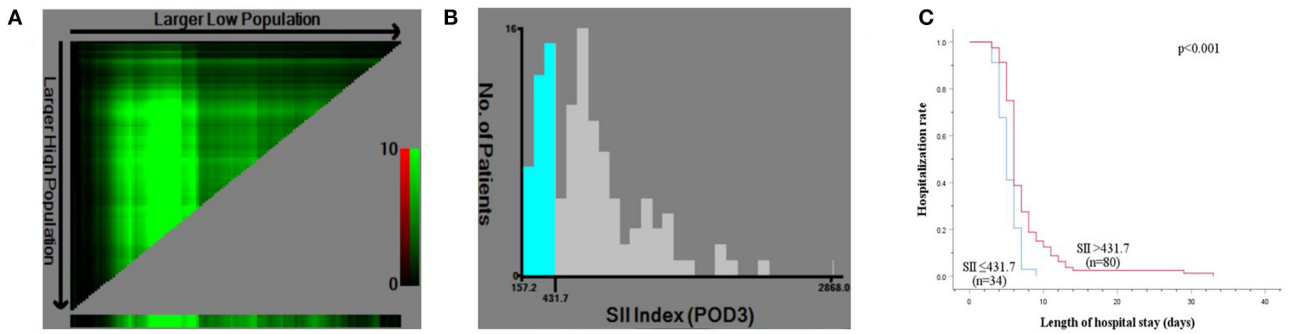

FIGURE 3 | X-tile analysis for calculating the cutoff point of SII on postoperative day (POD) 3. **(A)** X-tile plot of SII on POD 3. **(B)** The optimal cutoff point shown on a histogram of entire cohort. **(C)** Kaplan–Meier plot of association between SII ≤ 431.7 and hospitalization rate.

RESULTS OF THE META-ANALYSIS

Study Characteristics and Quality Assessment

The search strategy identified a total of 1,486 citations from the electronic databases. After removing duplicates and studies that did not fulfill the eligibility criteria, full-text review occurred for 56 studies. Of these, 12 studies (14–24) compared LRH with ORH for 1,315 patients diagnosed with recurrent liver tumors and provided complete data on patients' characteristics and surgical outcomes. There were 602 and 713 patients in the LRH and ORH, respectively. A flow diagram of the selection process was outlined in **Figure 4**. The characteristics of eligible studies are summarized in **Table 3**. Of the studies included, five were conducted in Japan, three in China, one in Europe, one in Singapore, one in France, and one in 42 liver surgery centers around the world. A summary of NOS scores of all studies is given in **Table 4**. Scores of all studies ranged from 7 to 8, which were assessed as high quality.

Surgical Outcomes of LRH vs. ORH

According to this meta-analysis, the intraoperative blood loss was significantly lower in the LRH than that in the ORH group (SMD = −0.79, 95% CI = −1.11 to −0.47, $P < 0.001$) (**Figure 5**). All these 12 studies had reported duration of surgery and postoperative hospital stay. The pooled data indicated that duration of hospital stay was reduced in the LRH group in comparison with that in the ORH group (SMD = −0.51, 95% CI = −0.79 to −0.22, $P < 0.001$) (**Figure 6**). However, the

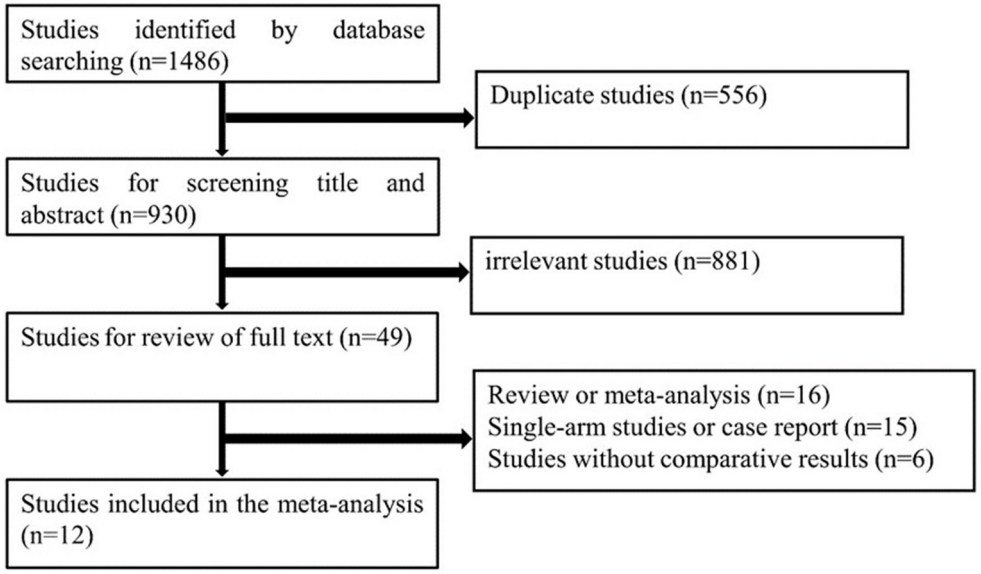

FIGURE 4 | Flow diagram of the selecting process.

operation time did not differ significantly between the two groups (SMD = −0.02, 95% CI = −0.28 to 0.23, $P = 0.86$) (**Figure 7**). Furthermore, nine studies had provided data of postoperative complications, with eight providing major complications. Overall complication rate did not differ significantly between the two groups (OR = 0.44, 95% CI = 0.19–1.03, $P = 0.06$) (**Figure 8**), whereas the major complications were significantly decreased in LRH group when compared to ORH group (OR = 0.35, 95% CI = 0.19–0.66, $P = 0.001$) (**Figure 9**). In addition, there were no significant differences in terms of transfusion rate (OR = 0.45, 95% CI = 0.19–1.10, $P = 0.08$) (**Figure 10**) and mortality (OR = 1.14, 95% CI = 0.44–2.92, $P = 0.79$) (**Figure 11**).

Publication Bias

The publication bias evaluation for the meta-analysis of operation time is shown in **Supplementary Figure 1**. There was no obvious asymmetry in the funnel plot. In addition, the Begg test ($P = 0.681$) and Egger test ($P = 0.942$) further showed that there was no potential publication bias among studies.

DISCUSSION

To explore the advantages of LRH over ORH in treating recurrent liver tumors, we performed the present PSM analysis to minimize the selection bias and then compared surgical outcomes between the two groups. The results indicated that LRH had obvious advantages, such as less intraoperative blood loss and use of Pringle maneuver. The reasons for reduced blood loss and use of Pringle maneuver were mainly the positive pressure of pneumoperitoneum and magnified view of laparoscopic approach. Moreover, patients undergoing LRH seems to have faster postoperative recovery because LRH was associated with better postoperative liver function and shorter hospital stay. Although the exact mechanism of enhanced recovery after LRH has not been elucidated clearly, we presumed that attenuation of postoperative inflammation might play an important role as the inflammation-based markers were significantly lower in LRH group. Pringle maneuver was more applied in ORH group, which may cause ischemia–reperfusion injury and postoperative liver dysfunction (26). Thus, how to minimize ischemia–reperfusion and maximize the protection of liver function should be one of the focuses in the surgery. We also demonstrated that SII $\leq$ 431.7 on POD 3 was associated with shorter hospital stay, which indicates this index may be practical in predicting the faster postoperative recovery. Interestingly, similar with published study, most of matched patients in our retrospective cohort were diagnosed with rHCC accompanied with liver cirrhosis, indicating that LRH can be a safe and efficient procedure for cirrhotic patients (27, 28). However, the operation time, blood transfusion rate, and incidence of postoperative complications in the LRH group were similar to those in the ORH group.

The first reported PSM analysis of LRH vs. ORH for rHCC suggested that there was significant difference in postoperative outcomes between two approaches, including lower morbidity rate, reduced blood loss, and shorter hospital stay in the LRH group (17). Contrary to that, a similar study comparing LRH and ORH for colorectal liver metastases failed to show difference of surgical outcomes except surgery-specific morbidity rate (18). The contradiction may derive from the difference in the baseline characteristics between these two diseases and various surgical skills and techniques, as well as the selection bias caused by the retrospective study design. Furthermore, those analyses did not include many possible remaining confounders into the PSM model, such as the location of tumors and approach to previous operation, which may influence the odds of conversion and other surgical outcomes. As previously reported, there were more

TABLE 3 | Summary of characteristics of included studies.

References	Study design	Country	Group	No.	Gender (M/F)	Age (years)	Child–Pugh grade (A/B)	Liver cirrhosis (yes/no)	Previous operation (OH/LH)	Tumor size (cm)	Pathology
Kanazawa et al. (14)	RM	Japan	Lap	20	15/5	70 (46–83)	19/1	7/13	15/5	1.7 (0.7–3.5)	HCC = 20
			Open	20	19/1	65 (43–74)	17/3	7/13	NA	2.2 (1.3–4.1)	HCC = 20
Chan et al. (15)	RM	China	Lap	11	8/3	61 (43–80)	11/0	8/3	6/5	2.0 (1.0–4.5)	HCC = 11
			Open	22	16/6	62 (43–76)	NA	NA	NA	2.0 (1.0–5,0)	HCC = 22
Zhang et al. (16)	P	China	Lap	31	26/5	54 (37–66)	NA	NA	31/0	2.5 ± 1.0	HCC = 31
			Open	33	27/6	59.5 (34–65)	NA	NA	33/0	3.8 ± 1.1	HCC = 33
Hallet et al. (18)	PSM	France	Lap	27	20/7	63.6 (59–70.9)	NA	NA	NA	NA	CRLM = 27
			Open	81	50/31	62.8 (57.5–70.3)	NA	NA	NA	NA	CRLM = 81
Liu et al. (17)	PSM	China	Lap	30	23/7	56.5 (27–79)	30/0	26/4	21/9	2.1 (1.0–5.0)	HCC = 30
			Open	30	28/2	48.5 (28–79)	27/3	26/4	NA	2.45 (1.0–4.3)	HCC = 30
Noda et al. (19)	R	Japan	Lap	20	15/5	68.8 ± 9.7	19/1	8/12	12/8	2.41 ± 1.26	HCC = 15/CRLM = 5
			Open	48	39/9	67.2 ± 8.4	44/4	16/32	46/2	2.21 ± 1.09	HCC = 36/CRLM = 12
Ome et al. (20)	R	Japan	Lap	33	26/7	73 (45–84)	33/0	13/20	21/12	1.80 (0.4–4.5)	HCC = 16/M = 15/B = 2
			Open	37	27/10	71 (45–84)	36/1	10/27	34/3	2.40 (0.7–5.5)	HCC = 16/M = 16/B = 2/CCC = 1/others = 2
Goh et al. (21)	PSM	Singapore	Lap	20	18/2	68.5 (67–71.75)	NA	7/13	7/13	2.00 (1.15–2.775)	HCC = 20
			Open	20	18/2	69 (63–72.25)	NA	7/13	NA	2.60 (1.50–3.0)	HCC = 20
Inoue et al. (22)	PSM	Japan	Lap	37	25/12	69 (45–86)	37/0	NA	NA	2.2 (0.8–5.2)	HCC/CCC = 18/others = 19
			Open	37	23/14	69 (42–81)	37/0	NA	NA	2.2 (0.5–4.3)	HCC/CCC = 19/others = 18
van der Poel et al. (23)	PSM	7 European countries	Lap	105	62/43	61 ± 10.7	NA	NA	66/39	2.8 (1.9–4.4)	CRLM = 105
			Open	105	62/43	62 ± 9.6	NA	NA	69/36	3.0 (2.0–4.0)	CRLM = 105
Onoe et al. (24)	R	Japan	Lap	30	23/7	70.9 (50–85)	30/0	6/24	21/9	1.25 (0.08–3.5)	HCC = 30
			Open	42	30/12	72.0 (59–88)	34/8	16/26	36/6	1.75 (0.5–6.0)	HCC = 42
Morise et al. (25)	PSM	42 liver surgery centers	Lap	238	181/57	67.1 ± 11.8	NA	177/61	181/57	2.75 ± 2.88	HCC = 238
			Open	238	184/54	66.4 ± 10.2	NA	174/64	187/51	2.77 ± 2.64	HCC = 238

OH, open hepatectomy; LH, laparoscopic hepatectomy; M, male; F, female; RM, retrospective matched cohort; Lap, laparoscopic; HCC, hepatocellular carcinoma; NA, not available; P, prospective cohort; PSM, propensity score–matched cohort; R, retrospective cohort; CRLM, colorectal liver metastasis; CCC, central cholangiocarcinoma; B, combined HCC and CCC.

TABLE 4 | Quality assessment using Newcastle–Ottawa Scale (NOS).

References	Selection (out of 4)				Comparability (out of 2)	Outcomes (out of 3)			NOS score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Exposure	Outcome of interest not present at start		Assessment of outcome	Follow-up	Adequacy of follow-up	
Kanazawa et al. (14)	*	*	*	*	**	*	Unclear	Unclear	7
Chan et al. (15)	*	*	*	*	**	*	Unclear	Unclear	7
Zhang et al. (16)	*	*	*	*	**	*	*	Unclear	8
Hallet et al. (18)	*	*	*	*	**	*	*	Unclear	8
Liu et al. (17)	*	*	*	*	**	*	*	Unclear	8
Noda et al. (19)	*	*	*	*	**	*	Unclear	Unclear	7
Ome et al. (20)	*	*	*	*	**	*	Unclear	Unclear	7
Goh et al. (21)	*	*	*	*	**	*	*	Unclear	8
Inoue et al. (22)	*	*	*	*	**	*	Unclear	Unclear	7
van der Poel et al. (23)	*	*	*	*	**	*	Unclear	Unclear	7
Onoe et al. (24)	*	*	*	*	**	*	Unclear	Unclear	7
Morise et al. (25)	*	*	*	*	**	*	*	Unclear	8

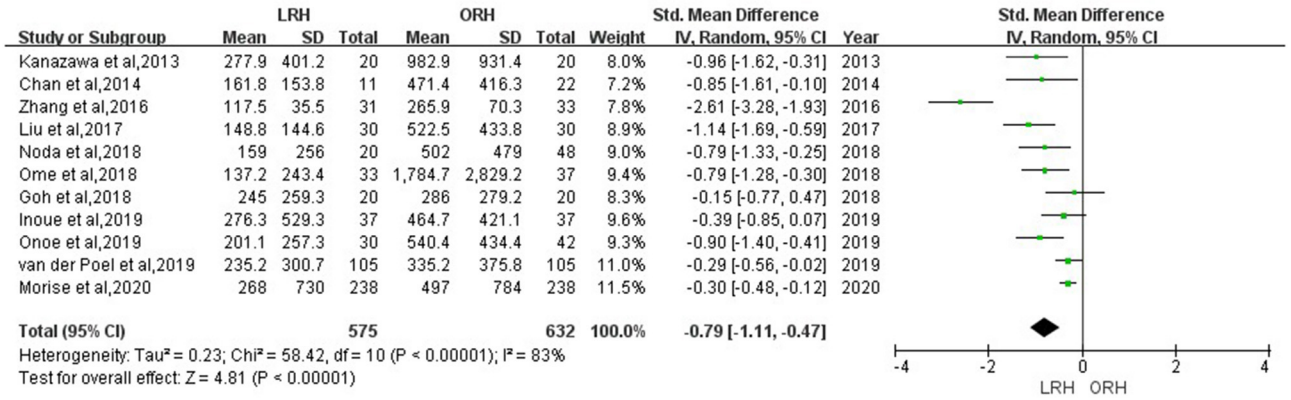

FIGURE 5 | Forest plots comparing blood loss between LRH group and ORH group.

severe adhesions if the previous hepatectomy was performed by open approach (29). Thus, the present PSM analysis built a model based on eight variables, including age, gender, tumor number, maximum tumor size, tumor location, liver cirrhosis, HBV infection status, and previous hepatectomy approach. After balancing the baseline characteristics using PSM, there was no apparent difference in postoperative morbidity between LRH and ORH.

In one recent meta-analysis performed by Liang et al., the multicenter propensity score–based analysis conducted by Morise et al. was not included, which comprises 476 matched patients (8, 25). To make the meta-analysis more convincing, we combined the results of the study above with those from 11 previous studies. Our analysis included 1,315 patients in total, which was almost twice the patients of the most recent meta-analysis. With the exception of major postoperative complications, the result of meta-analysis was comparable to the present propensity score–based study. As compared with ORH, LRH was associated with less blood loss and faster postoperative recovery with equivalent morbidity rate. The smaller wound and lower postoperative pain help patients walk sooner after operation, which then result in shorter hospital stay and enhanced recovery. These data have provided a more comprehensive conclusion regarding the safety and efficiency of LRH for the treatment of recurrent liver tumors.

As LRH presents more challenges because of intra-abdominal adhesions, especially in patients with severe portal hypertension, LH was considered a contraindication for recurrent liver tumors. Besides, Belli et al. reported that the selected patients for LRH should satisfy the following criteria: well-preserved liver function without signs of severe portal hypertension, a maximum size of 5 cm, and tumor located in anterolateral segments (30). However, with the improvement of laparoscopic surgical techniques and instruments, we also carried out LRH for rHCC located in

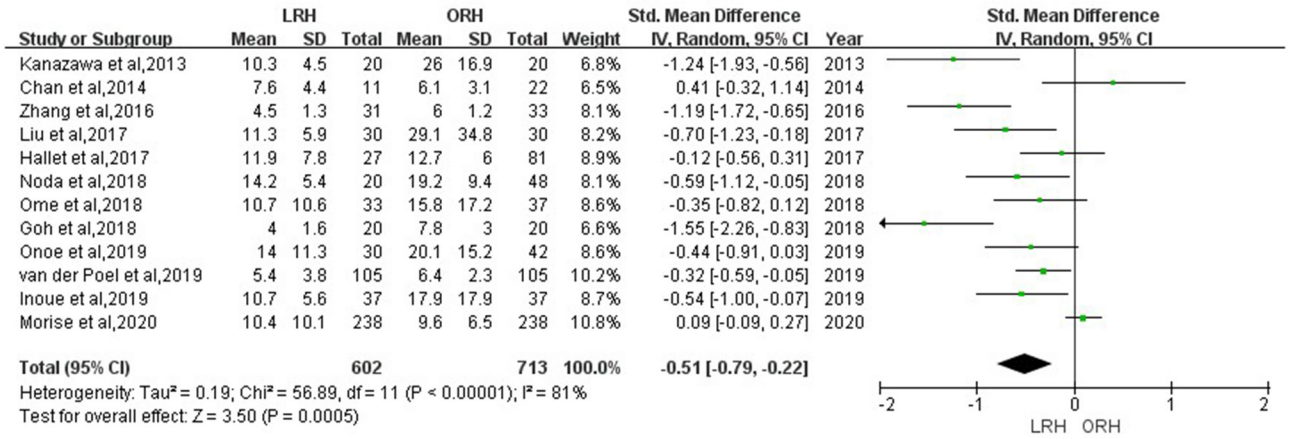

FIGURE 6 | Forest plots comparing hospital stay between LRH group and ORH group.

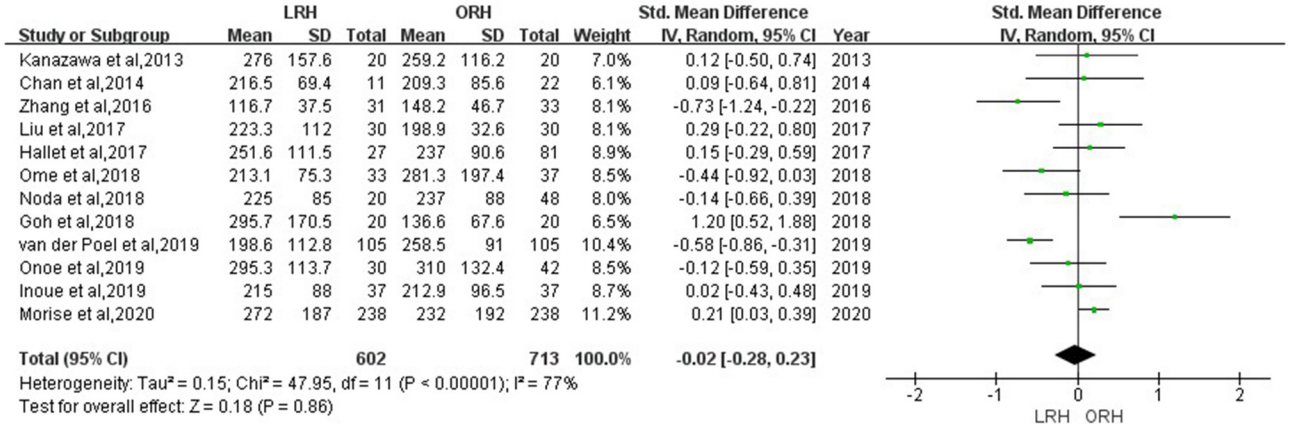

FIGURE 7 | Forest plots comparing operation time between LRH group and ORH group.

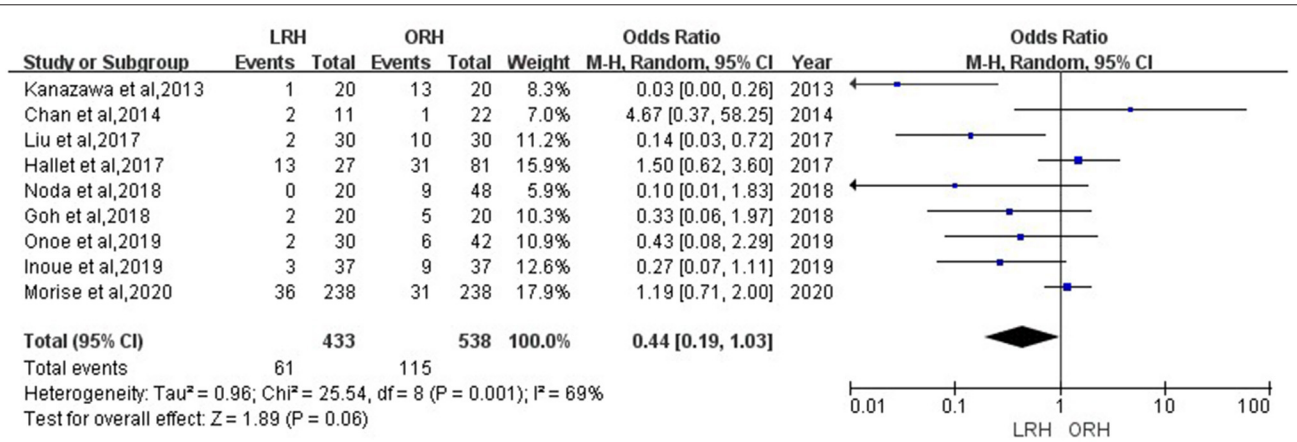

FIGURE 8 | Forest plots comparing overall postoperative complications rate between LRH group and ORH group.

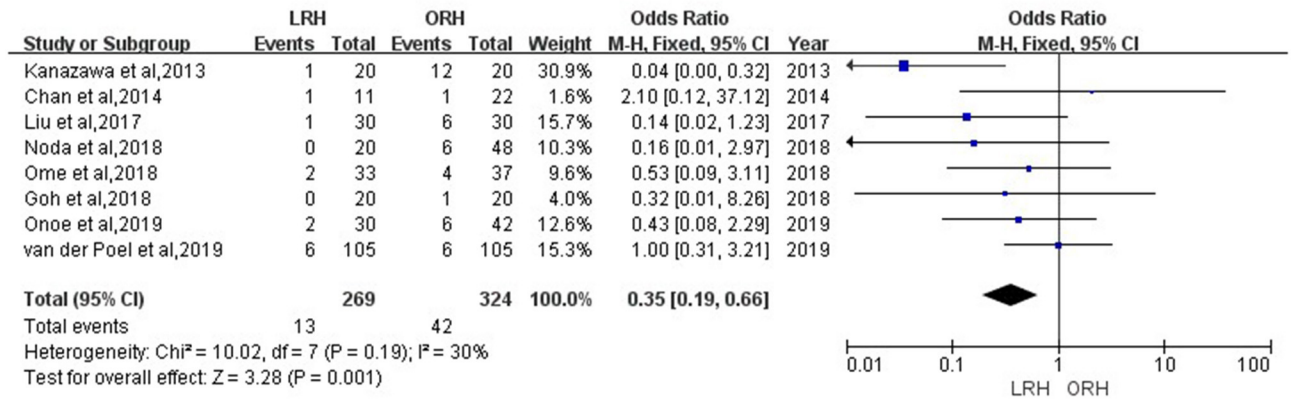

FIGURE 9 | Forest plots comparing major postoperative complications rate between LRH group and ORH group.

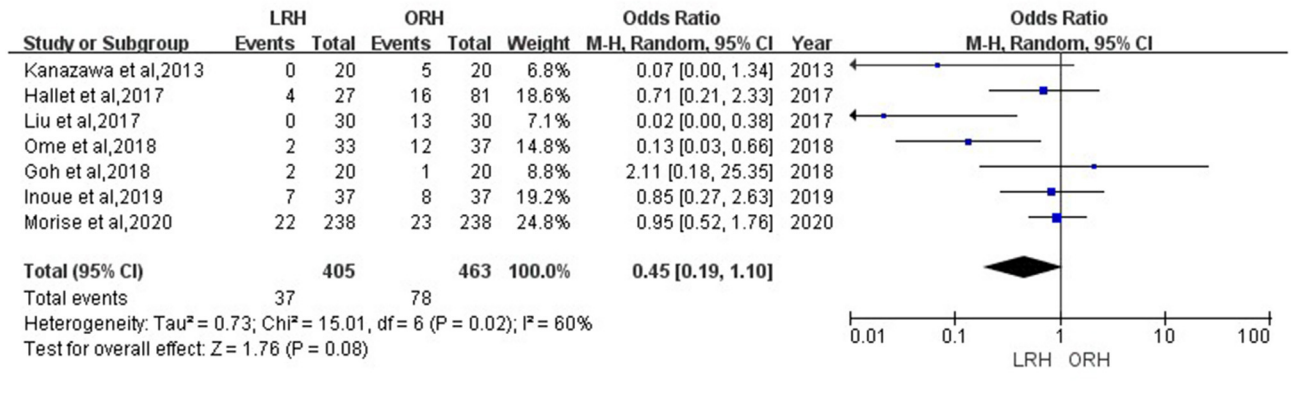

FIGURE 10 | Forest plots comparing blood transfusion rate between LRH group and ORH group.

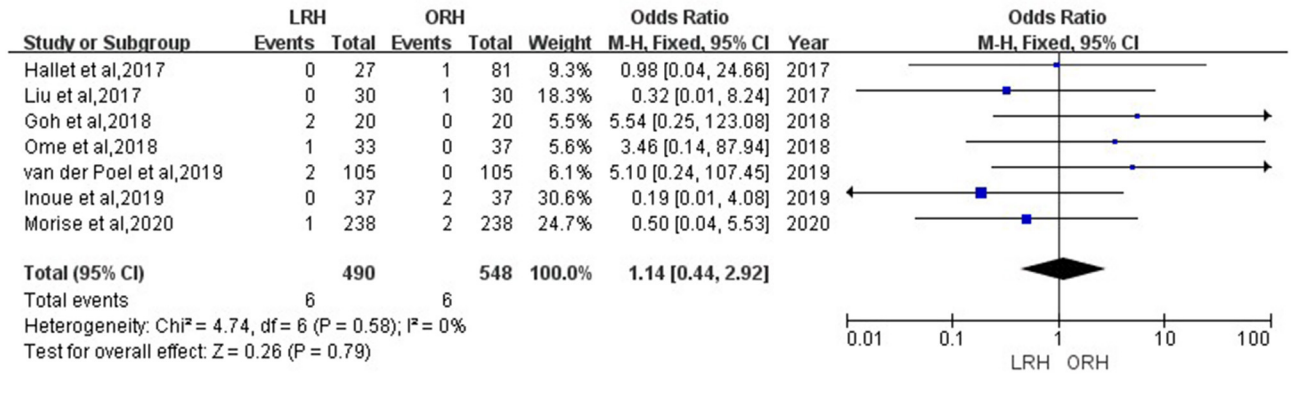

FIGURE 11 | Forest plots comparing mortality between LRH group and ORH group.

posterosuperior segments or rHCC with maximum size of >5 cm. It has been reported that LH could reduce formation of adhesions and damage to liver parenchyma, collateral vessels, and surrounding structures (31, 32). The pneumoperitoneum and magnified view of laparoscopic approach make the adhesiolysis more meticulous, contributing to less blood loss. In addition, LH was suggested for patients with poor liver function because of the advantages in surgical outcomes, including smaller incision and less hepatic mobilization and blood loss (25). Notwithstanding these advantages, the Southampton guidelines stated that LRH

should be performed by experienced surgeons and avoided in the early phase of learning curve (33). Besides, the proper trocar placement should be adjusted according to operation custom of the surgeon, as well as the changed liver anatomy and formed adhesions caused by previous hepatectomy. Moreover, for the consideration of future abdominal operations, it is better to avoid unnecessary extensive adhesiolysis when the adhesion does not affect the operative procedure (34, 35).

Although our study combined a PSM analysis with a meta-analysis in order to draw a more definitive conclusion, several limitations of this study must be considered. First, there are still selection biases in our own data as this study is a retrospective analysis of a single center. Despite the PSM analysis, the level of evidence still cannot compete with that of RCT because PSM cannot control for other potential confounders we do not include. Second, the included patients in our center are still under follow-up, and the data of long-term outcomes are not complete and adequate in our own study, as well as other published studies. Thus, we did not evaluate long-term oncologic outcomes in the present PSM analysis and meta-analysis. Third, most of the included studies in the meta-analysis were retrospective case series in a single center without proper patient randomization, which may be inclined to cause selection bias. Significant heterogeneity was found in some outcomes between the included studies, which may be attributed to study designs, characteristics of the patients, various surgical equipment and procedure, and different indications for LRH with recurrent liver tumors. In view of these limitations, studies with larger scale and RCTs with short- or long-term oncological outcomes should be carried out to further confirm the advantages of LRH.

CONCLUSIONS

We compared the perioperative outcomes of LRH and ORH for patients with recurrent liver tumors. Although there are several challenges mentioned previously, LRH can be an appropriate minimally invasive procedure to treat recurrent liver tumors for selected patients because it presents a similar risk of postoperative complications and a faster postoperative recovery. Nonetheless, standard procedure of LRH should be established, and further large-scale studies are required to determine specific indications of LRH for recurrent liver tumors.

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 Zhongshan Hospital of Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-FC, X-YW, JF, and Z-BD conceived and designed the study. J-FC, X-TF, ZG, Y-HS, ZT, W-RL, XZ, KS, QG, and G-YD participated in the database search, data collection, and quality assessment. J-FC, X-TF, ZG, Y-HS, ZT, W-RL, XZ, QG, and JZ performed the statistical analysis. J-FC, X-TF, and ZG edited the paper. All authors provided critical revision of article and final approval of article.

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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.2021.646737/full#supplementary-material

Supplementary Figure 1 | Funnel plot of publication bias based on studies reporting operation time.

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Transarterial Chemoembolization Combined With Radiofrequency Ablation *Versus* Repeat Hepatectomy for Recurrent Hepatocellular Carcinoma After Curative Resection: A 10-Year Single-Center Comparative Study

Xin Zheng[1], *Yanqiao Ren*[2,3], *Hanqing Hu*[1] *and Kun Qian*[2,3]*

[1] Department of Hepatopancreatobilary Surgery, The First College of Clinical Medical Sciences, China Three Gorges University, Yichang, China, [2] Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [3] Hubei Province Key Laboratory of Molecular Imaging, Wuhan, China

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Edited by:
Alessandro Vitale,
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***Correspondence:**
Kun Qian
kunchien@163.com

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Background: The purpose of this study was to compare the efficacy and safety of transarterial chemoembolization (TACE) in combination with radiofrequency ablation (RFA) (TACE-RFA) and repeat hepatectomy in the treatment of recurrent hepatocellular carcinoma (HCC) after curative resection.

Methods: This retrospective study evaluated consecutive medical records of patients who received either TACE-RFA or repeat hepatectomy between January 2010 and May 2021. Overall survival (OS), progression-free survival (PFS), and complications were compared.

Results: Of the 2672 patients who received either TACE-RFA or repeat hepatectomy, 111 eligible patients were included in our study, 63 in the TACE-RFA group and 48 in the repeat hepatectomy group. The median OS was 38 months in the TACE-RFA group and 42 months in the repeat hepatectomy group, with no statistically difference between the two groups (P=0.45). Meanwhile, there was also no statistically significant difference in PFS between the two groups (P=0.634). Although both groups achieved similar outcomes, the rate of major complications was significantly higher in the repeat hepatectomy group (P=0.003).

Conclusions: Patients with recurrent HCC in the TACE-RFA group and the repeat hepatectomy group had similar OS and PFS regardless of the patient's tumor diameter, but the TACE-RFA group was safer and more minimally invasive.

Keywords: recurrent hepatocellular carcinoma, transarterial chemoembolization, radiofrequency ablation, repeat hepatectomy, overall survival, progression-free survival

INTRODUCTION

Hepatocellular carcinoma is the most frequent liver cancer, and liver cancer is the fifth most common cancer and the second most common cause of cancer-related death worldwide (1). Curative hepatectomy is one of the best first-line treatments for specific patients. Median survival after curative hepatectomy for HCC patients has been reported to be 50-70 months (2–4). However, the presence of intrahepatic recurrence and *de novo* tumor in the residual liver after curative hepatectomy is common, with a reported 5-year recurrence rate as high as 70%-80% (5). In addition, cirrhosis, tumors larger than 5 cm in diameter, positive histological margins, or portal vein invasion has been demonstrated to be potential risk factors for recurrence (6, 7). Although this is a common clinical manifestation, there are still no clear global algorithms or guidelines on the management of recurrent HCC after hepatectomy, which remains a thorny issue that currently confounds clinicians and patients.

For recurrent HCC, repeat hepatectomy or salvage liver transplantation may be the best treatment. Repeat hepatectomy is reported to be an effective and safe treatment option (8–10). However, surgical treatment is not indicated for most of these patients because of limited reserve of liver function in the residual liver, intrahepatic multiple recurrences, postoperative adhesion, or lack of a liver donor (11, 12). Therefore, only a few patients benefit from curative treatments, which may create an incentive to explore other therapies and methods.

Transarterial chemoembolization (TACE), which combines targeted chemotherapy with arterial embolization, is a well-tolerated procedure with limited hepatotoxicity and is effective in patients with recurrent HCC with borderline liver function (13, 14). However, it has been reported that TACE alone is difficult to cause complete tumor necrosis even if the tumor diameter is small (15, 16). It has been reported that the combination of TACE and radiofrequency ablation (RFA) has the following theoretical advantages (17, 18): (1) TACE can reduce the heat sink effect, thereby increasing the ablation range; (2) Satellite lesions can be detected through TACE, which is more beneficial to RFA. As described by the theoretical advantages, many studies (19, 20) have also reported satisfactory effects of TACE combined with RFA (TACE-RFA) in the treatment of HCC.

Currently, there are studies (21, 22) comparing the efficacy of surgical resection and TACE in the treatment of recurrent HCC, and there are also studies (23, 24) comparing the efficacy of surgical resection and RFA in the treatment of recurrent HCC. However, to our knowledge, there are few reports on the efficacy of repeat hepatectomy and TACE-RFA in the treatment of recurrent HCC after resection. Thus, the purpose of this retrospective study was to compare the efficacy and safety of TACE-RFA and repeat hepatectomy in the treatment of recurrent HCC. In addition, Peng et al (25) concluded that TACE-RFA had a similar effect to hepatectomy for recurrent HCC with a diameter of < 5cm, but for recurrent HCC with a tumor diameter of > 5cm, it has not been reported so far. Hence, another purpose of this study was to investigate the efficacy of TACE-RFA and hepatectomy for recurrent HCC with a diameter of more than 5cm.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective comparative study was approved by the local hospital ethic committee. Written informed consent was obtained from all patients prior to treatment.

From January 2010 to May 2020, 2672 patients with recurrent HCC after hepatectomy were admitted to our hospital. Before these patients were treated, the treatment strategy was recommended by the multidisciplinary oncology committee. Repeat hepatectomy was recommended based on the same criteria as initial resection, including Child-Pugh class A patients with solitary or oligonodular (2-3 nodules < 3cm) recurrence, preserved liver function, and sufficient liver volume (the residual liver volume after repeat hepatectomy must be more than 40% of the standard liver volume) without severe portal hypertension. TACE-RFA was considered in patients with Child-Pugh class A or B, no vascular involvement, and no severe ascites, and when repeated hepatectomy was not possible due to insufficient hepatic reserve function. Meanwhile, the time of RFA after TACE depends on the disappearance of complications and recovery of liver function after embolization. In our center, RFA is usually performed 1-2 weeks after TACE.

The diagnosis of recurrent HCC was based on the diagnostic criteria of the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (26). A total of 111 consecutive patients who received either TACE-RFA (n=63) or repeat hepatectomy (n=48) meeting the following inclusion criteria were enrolled in the study: (1) first intrahepatic recurrence after the curative resection; (2) Child-Pugh class A or B; (3) no evidence of invasion into the macroscopic vascular, extrahepatic metastasis, or uncontrolled ascites; (4) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and expected survival of >3 months; (5) patients who refuse to undergo liver transplantation. The patient was excluded if the exclusion criteria were met: (1) had previously received any treatment for recurrent HCC; (2) hepatic dysfunction (total bilirubin serum >3 mg/dL, serum albumin level <2.0 mg/dL, INR > 1.5), renal impairment (serum creatinine level >2mg/dL); (3) uncontrolled infection.

TACE

Conventional transarterial chemoembolization (cTACE) was performed by two experienced interventional radiologists according to our institutional standard protocol (19, 27). Briefly, in all TACE procedures, angiography of the celiac trunk and superior mesenteric artery was performed to visualize the arterial vascularization of the liver and to evaluate portal vein patency. The epirubicin-lipiodol emulsion, which prepared by dissolving 60 mg/m2 of epirubicin in 1–2 ml of a 2% lidocaine, before mixing with 5–20 ml lipiodol was delivered directly into the feeding artery under fluoroscopic guidance, after

placing the catheter tip in the distal feeding arteries as close to the tumor as possible using either the standard 5 Fr catheter or a 3 Fr coaxial catheter when necessary, followed by the injection of 300-500um gelatin sponge particles. The endpoint of embolization was the tumor vessels were completely filled with the drugs and the tumor stain disappeared on angiographic imaging.

RFA

The RFA procedure was performed in accordance with the standard treatment regimen described in our previous study (19). In short, percutaneous RFA was performed using a RITA 1500 generator (RITA Medical Systems, Mountain View, CA, USA) under real-time ultrasound and or both CT guidance, and different needle electrodes were used as follows: For tumors <= 2.0 cm in diameter, a single extendable electrode was used; otherwise, a multi-electrode was used. And to accomplish a safe range of 0.5–1.0 cm, multiple overlapping ablation zones were demanded. Single or multiple overlapping ablations were performed to achieve an ablation zone with at least a 0.5–1.0 cm ablative margin around the tumor. After the RFA procedure, the intrahepatic needle track was cauterized during electrode retraction to prevent bleeding or tract seeding.

Repeat Hepatectomy

The liver function was evaluated by Child-Pugh scoring system before repeat hepatectomy. Among all patients who underwent repeat hepatectomy, 42 patients (87.5%) were Child-Pugh A stage and 6 patients (12.5%) was Child-Pugh B stage. Due to the serious abdominal adhesion during the repeat operation and in order to minimize the occurrence of complications, we chose an open operation. Patients were informed of the risks of the surgery before consent for the operation was obtained. Surgical resection was carried out in a standard procedure by a surgical team consisting of three experienced surgeons who had more than 10 years of experience in hepatectomy. The operating procedure is briefly as the liver is accessed by a right subcostal incision with midline extension, followed by intraperitoneal exploration to exclude disseminated disease. After initial mobilization of the falciform ligament, the liver is fully separated from the triangular and coronary ligament connecting the liver and diaphragm. Intraoperative ultrasound within the parenchyma localizes all suspected tumor nodules and identifies the portal vein and the liver veins. After this, the first porta hepatis occlusion band was preset, the portal vein was dissected, and the portal vein branch of the hepatic segment where the tumor was located was blocked. Then pre-excision line was marked according to the ischemia line, and the liver was cut by ultrasonic scalpel and bipolar cautery, then test with lipofundin is performed by retrograde flushing over the remaining cystic duct and obstruction of the main hepatic duct to detect and close the bile leakage at the transection surface. The transection surface is hemostased by coagulation with an argon beamer and bipolar cautery.

Definition and Evaluation of Data

Overall survival (OS) referred to the interval between the first TACE procedure or repeat hepatectomy and the date of death or last follow-up. Progression-free survival (PFS) was known as the period between the date of the first TACE procedure or repeat hepatectomy and the date of progression for patients who displayed radiologic evidence of disease progression or the date of death. Complications or side effects were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0). Major complications were events leading to death and disability, which increase the level of care, or result in hospital admission, or substantially prolong the length of hospitalization (28).

Follow-Up

All patients were followed up until May 2021. Patients in both groups were evaluated 4 to 6 weeks after treatment. Reexamination included laboratory tests (hematology and biochemical markers) and abdominal contrast-enhanced CT or magnetic resonance (MR). CT or MR imaging at 4-6 weeks after initial treatment were compared with preoperative imaging, and objective tumor radiologic regression (ORR) and disease control rate (DCR) were determined in both groups according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) (29). ORR referred to complete response (CR) or partial response (PR). DCR represented CR, PR or stable disease (SD). During the follow-up period, tumor recurrence was divided into local recurrence, intrahepatic recurrence and extrahepatic metastasis. Local recurrence is defined as the presence of tumors in or around the primary lesion. Intrahepatic recurrence refers to the new lesion being more than 2.0 cm away from the primary lesion. Extrahepatic metastasis refers to extrahepatic tumor lesions. When residual viable HCCs or recurrent tumors, intrahepatic distant metastasis or extrahepatic metastasis occurred during the follow-up period, patients were given corresponding treatments such as resection, RFA, TACE, sorafenib and conservative treatment according to the characteristics of tumor recurrence, liver function status and patient requirements. Imaging (contrast-enhanced CT or MR) and laboratory examinations were performed every 2-3 months and patients were followed up until death or the end of the study's follow-up.

Statistical Analyses

SPSS software (Version 24.0; IBM, Armonk, New York) was used for all statistical analyses, and $P < 0.05$ indicated a statistically significance. Discrete variables were represented by numbers with percentages were calculated by Chi-square test, and continuous variables were presented as mean ± standard deviation. Kaplan-Meier method was used to evaluate the differences in OS and PFS between the two groups. The 95% confidence interval (CI) was calculated for median OS, median PFS, and hazard ratio (HR). Log-rank test was used for univariate analysis, in which variables with P value less than 0.10 in univariate analysis were added to multivariate analysis. Potential prognostic variables affecting OS and PFS were calculated using a Cox proportional hazard regression model.

RESULTS

Study Population and Patient Characteristics

From January 2010 to May 2020, a total of 2672 patients received TACE-RFA or repeat hepatectomy, and 2561 patients were excluded because they did not meet the research requirements, as shown in **Figure 1**. Finally, a total of 111 recurrent HCC patients were enrolled in this study, 63 of whom received TACE-RFA and 48 of whom received repeat hepatectomy. There were 55 males (87.3%) and 8 females (12.7%) in the TACE-RFA group, with an average age of 53.1 ± 12.7 years old. There were 39 males (81.3%) and 9 females (18.7%) in the repeat hepatectomy group, with an average age of 52.0 ± 12.5 years old. There was no significant difference in baseline data between the two groups (**Table 1**).

The median follow-up period was 34 months (range, 4–106 months) in the TACE-RFA group and 30.5 months (range, 0–92 months) in the repeat hepatectomy group. In the TACE-RFA group, 48 (76.2%) patients died during the observation period, and in the repeat hepatectomy group, 29 (60.4%) patients died.

Treatment Response and Recurrence

The morphologic response of target lesions was verified using abdominal contrast-enhanced CT or MR imaging. In the TACE-RFA group, 17 patients achieved CR, 25 patients achieved PR, and 11 patients achieved SD. Hence, the ORR and DCR in the TACE-RFA group were 66.7% and 84.1%, respectively. Meanwhile, during the period of follow-up, in the TACE-RFA group, a total of 43 patients (68.3%) had recurrence, including 11 patients (17.5%) with local recurrence, 25 patients (39.7%) with intrahepatic recurrence, 7 patients (11.1%) with extrahepatic metastases, and a total of 30 patients (62.5%) had recurrence in the repeat hepatectomy group, including 6 patients (12.5%) with local recurrence, 19 patients (39.6%) with intrahepatic recurrence, 5 patients (10.4%) with extrahepatic metastases. There was no significant difference in recurrence rate between the two groups (P=0.527).

Overall Survival

The median OS was 38 months (95%CI: 28.9 months, 47.1 months) in the TACE-RFA group and 42 months (95%CI: 26.6months, 57.4 months) in the repeat hepatectomy group, with no statistically significant difference between the two groups (P= 0.45, **Figure 2**). Although univariate analysis (**Table 2**) revealed that tumor number, α-Fetoprotein level, and Barcelona Clinic Liver Cancer (BCLC) stage were associated with OS, when these three factors were included in multivariate analysis (**Table 3**), none of them was an independent prognostic factor for OS (P>0.05).

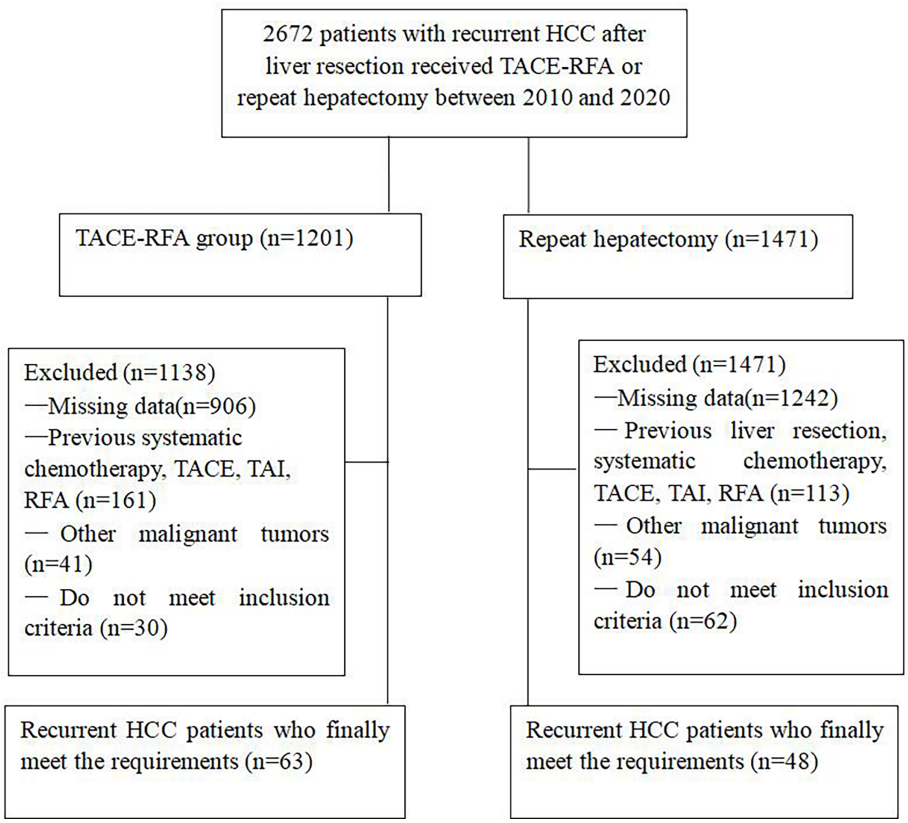

FIGURE 1 | Flow chart shows the screening procedure for recurrent HCC patients after curative resection.

TABLE 1 | Baseline characteristics.

Characteristics	TACE-RFA (N=63) (No, %; Mean ± SD)	Repeat hepatectomy (N=48) (No, %; Mean ± SD)	*P* value
Gender			0.38
Male	55 (87.3%)	39 (81.3%)	
Female	8 (12.7%)	9 (18.7%)	
Age (years)	53.1 ± 12.7	52.0 ± 12.5	0.63
Bilirubin (μmol/L)	16.8 ± 8.3	17.9 ± 13.9	0.60
Albumin (g/L)	38.2 ± 5.4	38.6 ± 4.8	0.65
PT(s)	14.1 ± 1.4	14.3 ± 1.9	0.55
AST (μmol/L)	38.9 ± 17.4	34.6 ± 13.9	0.17
ALT (μmol/L)	35.7 ± 18.0	33.0 ± 15.8	0.42
Tumor size	4.0 ± 3.0	3.9 ± 2.2	0.86
Tumor number	1.48 ± 0.97	1.38 ± 0.64	0.53
Hepatitis			0.91
Hepatitis B	52 (82.5%)	40 (83.3%)	
Other	11 (17.5%)	8 (16.7%)	
α-Fetoprotein level			0.24
>400 ng/mL	28 (44.4%)	16 (33.3%)	
≤400 ng/ml	35 (55.6%)	32 (66.7%)	
Child-Pugh score			0.82
A	56 (88.9%)	42 (87.5%)	
B	7 (11.1%)	6 (12.5%)	
BCLC			0.14
A	39 (61.9%)	36 (75.0%)	
B	24 (38.1%)	12 (25.0%)	
Interval of recurrence from initial treatment (months)	22.5 ± 19.4	22.1 ± 19.5	0.93

TACE, Transcatheter arterial chemoembolization; RFA, Radiofrequency ablation; SD, Standard deviation; PT, Prothrombin time; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer.

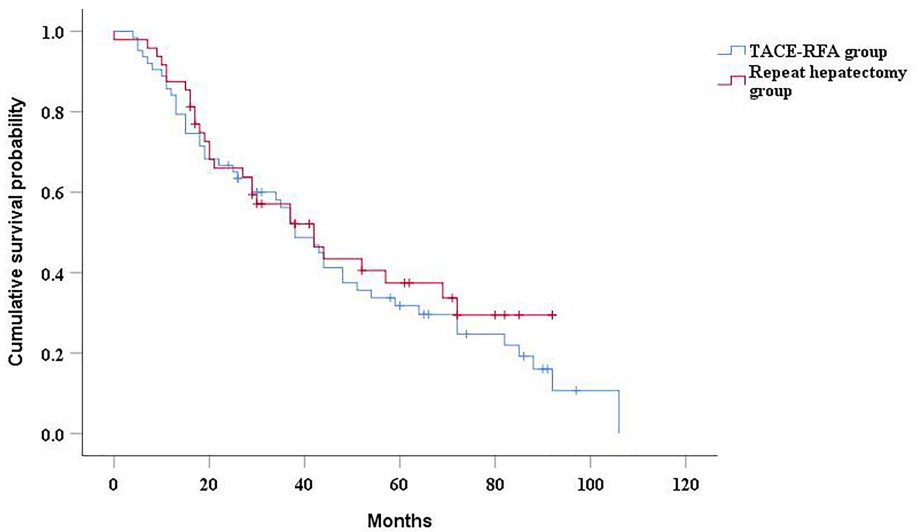

FIGURE 2 | Kaplan-Meier curves of cumulative survival in recurrent HCC patients who received TACE-RFA or repeat hepatectomy.

Progression-Free Survival

The median PFS of the TACE-RFA group was 24 months (95%CI: 15.2months, 32.8 months), and the median PFS of the repeat hepatectomy group was 21 months (95%CI: 13.4months, 28.6 months), with no significant difference between the two groups (*P*=0.634) (**Figure 3**). Univariate analysis (**Table 2**) indicated that bilirubin, tumor number, α-Fetoprotein level, and BCLC stage were associated with PFS. These four factors were included in multivariate

TABLE 2 | Univariate analysis of prognostic factors for overall survival and progression-free survival.

Variables	OS		PFS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	1		1	
Female	1.058 (0.557, 2.010)	0.863	1.098 (0.580, 2.079)	0.774
Age (years)	1.001 (0.983, 1.019)	0.922	1.001 (0.983, 1.019)	0.955
Bilirubin (μmol/L)	0.990 (0.966, 1.014)	0.423	0.975 (0.950, 1.002)	0.064
Albumin (g/L)	0.992 (0.950, 1.036)	0.715	1.002 (0.962, 1.044)	0.920
PT (s)	1.056 (0.943, 1.182)	0.345	1.058 (0.944, 1.187)	0.329
AST (μmol/L)	1.007 (0.993, 1.022)	0.306	0.999 (0.984, 1.014)	0.907
ALT (μmol/L)	1.003 (0.989, 1.017)	0.686	1.002 (0.988, 1.016)	0.783
Tumor size	1.017 (0.943, 1.096)	0.664	1.025 (0.951, 1.104)	0.522
Tumor number	1.487 (1.139, 1.942)	0.004	1.625 (1.251, 2.110)	0.000
Hepatitis				
Hepatitis B	1		1	
Other	0.839 (0.443, 1.591)	0.591	1.222 (0.672, 2.220)	0.511
α-Fetoprotein level				
≥400 ng/mL	1		1	
<400 ng/ml	1.611 (0.999, 2.598)	0.050	1.683 (1.059, 2.674)	0.028
Child-Pugh score				
A	1		1	
B	1.223 (0.606, 2.466)	0.574	0.880 (0.453, 1.710)	0.706
BCLC stage				
B	1			
A	1.686 (0.940, 3.023)	0.080	1.942 (1.082, 3.421)	0.026
Interval of recurrence from initial treatment (months)	1.000 (0.988, 1.012)	0.970	1.002 (0.990, 1.014)	0.728
Treatment method				
Repeat hepatectomy	1		1	
TACE-RFA	1.193 (0.750, 1.897)	0.456	1.113 (0.710, 1.743)	0.640

OS, Overall survival; PFS, Progression-free survival; HR, Hazard ratio; CI, Confidence interval; PT, Prothrombin time; AST, Aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; TACE, Transcatheter arterial chemoembolization; RFA, Radiofrequency ablation.

TABLE 3 | Multivariate analysis of prognostic factors for overall survival.

Variables	HR (95% CI)	*P* value
Tumor number	1.288 (0.831, 1.996)	0.258
α-Fetoprotein level		
>400 ng/mL	1	
≤400 ng/ml	1.673 (0.869, 3.219)	0.123
BCLC stage		
B		
A	1.235 (0.570, 2.679)	0.593

HR, Hazard ratio; CI, Confidence interval; BCLC, Barcelona Clinic Liver Cancer.

analysis, and the results demonstrated that tumor number was an independent prognostic factor affecting PFS (**Table 4**).

Subgroup Analysis by Tumor Size

In the subgroup analysis, there was no significant difference in median OS between the TACE-RFA group and the repeat hepatectomy group for recurrent HCC patients with tumor diameter less than 5cm (43 months *vs* 42 months, *P*=0.268) (**Figure 4A**). Similarly, there was no statistically significant difference in median PFS between the two groups (25 months *vs* 23 months, *P*=0.27) (**Figure 4B**). There was also no difference in median OS (26 months *vs* 19 months, *P*=0.713) (**Figure 5A**) and PFS (14 months *vs* 15 months, *P*=0.937) (**Figure 5B**) between the two groups for recurrent HCC patients with tumor size larger than 5cm.

Complications

One patient in the repeat hepatectomy group died of massive hemorrhage after surgery, while no treatment-related death occurred in the TACE-RFA group. In addition, liver failure occurred in 5 patients and gastrointestinal bleeding occurred in 4 patients in the hepatectomy group. The incidence of major complications was higher in the repeat hepatectomy group than in the TACE-RFA group (*P*=0.003) (**Table 5**). Similarly, there was a higher rate of minor complications in the repeat hepatectomy group. Fever and abdominal pain were the most common minor complications, and symptoms improved significantly after symptomatic management.

DISCUSSION

It has been reported that TACE can reduce hepatic arterial blood flow, thereby reducing heat sink effect and increasing the efficacy of RFA. Meanwhile, TACE can detect satellite lesions, which is beneficial to RFA (19). Hence, the combination of TACE and RFA was supposed to improve survival of recurrent HCC

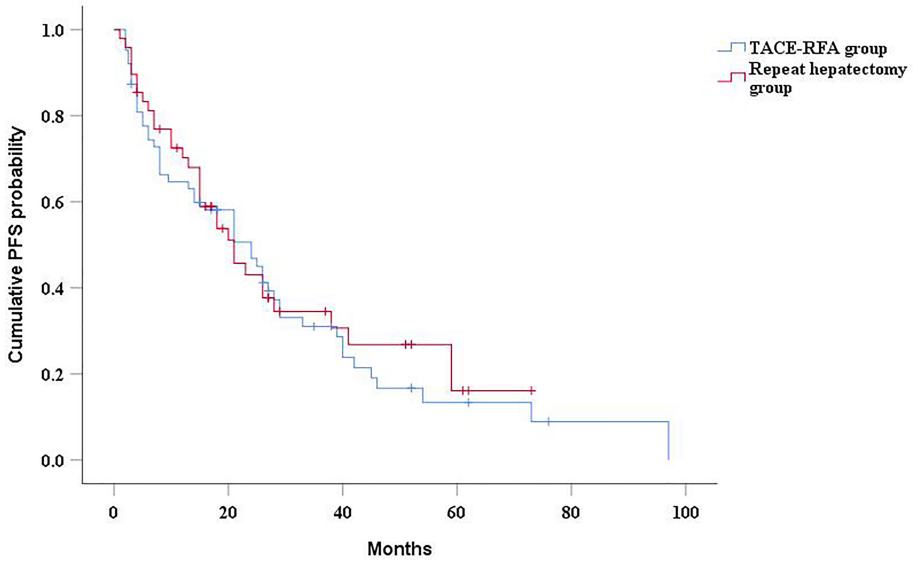

FIGURE 3 | Kaplan-Meier curves of PFS in recurrent HCC patients who received TACE-RFA or repeat hepatectomy.

TABLE 4 | Multivariate analysis of prognostic factors for time to progression.

Variables	HR (95% CI)	*P* value
Bilirubin (μmol/L)	1.022 (0.987, 1.058)	0.223
Tumor number	1.951 (1.246, 3.056)	0.004
α-Fetoprotein level		
>400 ng/mL	1	
≤400 ng/ml	1.717 (0.883, 3.338)	0.111
BCLC stage		
A		
B	1.014 (0.476, 2.162)	0.971

HR, Hazard ratio; CI, Confidence interval; BCLC, Barcelona Clinic Liver Cancer.

patients. The results of this study indicated that TACE-RFA achieved similar local efficacy and survival outcomes in patients with recurrent HCC compared with repeat hepatectomy, with no significant difference in OS and PFS between the two groups. Therefore, TACE-RFA may be a better choice for recurrent HCC patients who are not suitable for reoperation.

Song et al. retrospectively analyzed the clinical data of patients with recurrent HCC after hepatic resection who received TACE-RFA or TACE alone, and the results showed that TACE-RFA achieved better PFS than patients in the TACE alone group (30). Meanwhile, Peng et al. compared the efficacy of TACE-RFA with repeat hepatectomy in the treatment of recurrent HCC and concluded that TACE-RFA provided comparable OS and PFS compared with repeat hepatectomy (25). Similarly, our results also showed that TACE-RFA can achieve satisfactory results. This suggests that combination therapy, as described by the theoretical advantage, has a synergistic effect and is beneficial for patients with recurrent HCC.

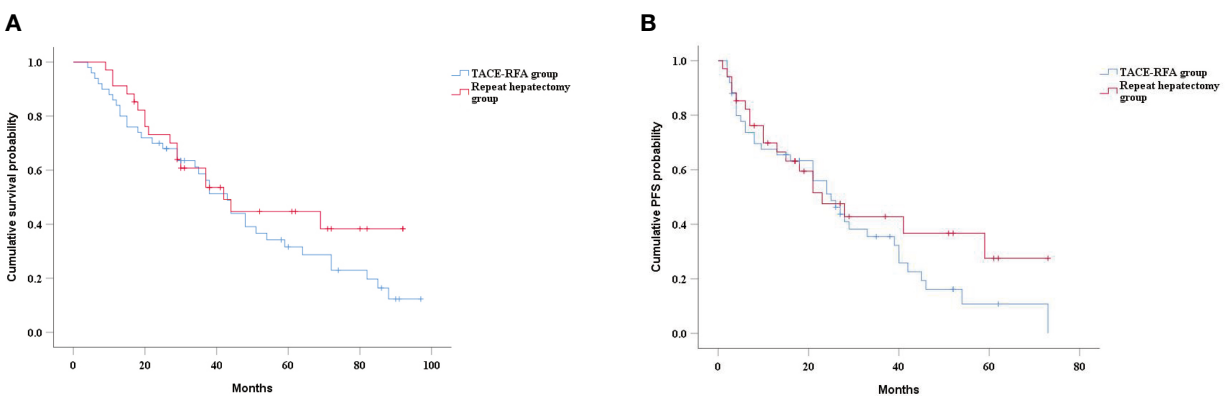

FIGURE 4 | Kaplan-Meier curves of cumulative survival **(A)** and PFS **(B)** in in patients with tumors smaller than 5cm in diameter.

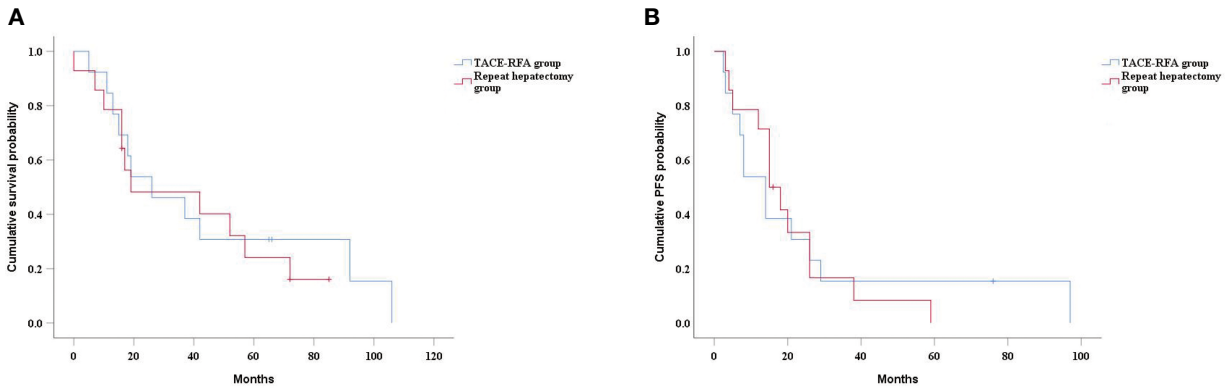

FIGURE 5 | Kaplan-Meier curves of cumulative survival **(A)** and PFS **(B)** in in patients with tumors larger than 5cm in diameter.

TABLE 5 | Complications after treatment.

Variable	TACE-RFA (N=63) (No, %)	Repeat hepatectomy (N=48) (No, %)	*P* value
Major complication	4 (6.3%)	13 (27.1%)	0.003
Mortality	0	1 (2.1%)	
Liver failure	2 (3.2%)	5 (10.4%)	
Gastrointestinal hemorrhage	1 (1.6%)	4 (8.3%)	
Abdominal pain			
Grade 3	1 (1.6%)	2 (4.2%)	
Vomiting			
Grade 3	0	1 (2.1%)	
Minor complication			
Fever			
Grade 1	15 (23.8%)	21 (43.8%)	0.026
Grade 2	8 (12.7%)	13 (27.1%)	0.055
Abdominal pain			
Grade 1	20 (31.7%)	27 (56.3%)	0.01
Grade 2	12 (19.0%)	19 (39.6%)	0.017
Vomiting			
Grade 1	11 (17.5%)	16 (33.3%)	0.053
Grade 2	6 (9.5%)	8 (16.7%)	0.261

TACE, Transcatheter arterial chemoembolization; RFA, Radiofrequency ablation.

However, in the study of Song (30) and Peng et al. (25), all patients with recurrent HCC had tumor diameters of less than 5cm, while for patients with recurrent HCC with tumor diameters of more than 5cm, no study has reported the efficacy of TACE-RFA and repeat hepatectomy in these patients. In this study, subgroup analysis results indicated that TACE-RFA and repeat hepatectomy had similar OS and PFS for recurrent HCC with tumor diameter greater than 5cm, indicating that TACE-RFA also had a satisfactory effect for recurrent HCC with tumor diameter greater than 5cm.

Although our study also demonstrated that TACE-RFA and repeat hepatectomy had similar therapeutic effects, complications should not be ignored in the choice of treatment modality for patients with recurrent HCC. In this study, the incidence of major complications in the repeat hepatectomy group was significantly higher than that in the TACE-RFA group. It was reported that the incidence of major complications in repeat hepatectomy was 6%-24.4% (31, 32), and the incidence of major complications in this study was 27.1%, slightly higher than the results reported in other studies. This may be because the tumor diameter of some HCC patients in this study was larger than 5cm, and the larger the tumor diameter was, the more likely it was to lead to complications. This also suggested that TACE-RFA may be a safer and less invasive treatment for patients with recurrent HCC.

This study was a retrospective study, so the non-randomized design was a major limitation of the study. Therefore, it is necessary to conduct prospective multicenter randomized controlled trial to verify our results. Meanwhile, no propensity matching analysis was conducted in this study, because the number of patients in this study was limited, and there was no significant difference in baseline data between the two groups.

CONCLUSIONS

In conclusion, compared with repeat hepatectomy, TACE-RFA has the comparable local efficacy and long-term survival results for patients with recurrent HCC after hepatectomy. Meanwhile, TACE-RFA has also achieved satisfactory results for patients with tumor diameter greater than 5cm. In addition, patients in the TACE-RFA group had relatively fewer complications.

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 Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XZ, YR, and HH collected the patients' data. XZ drafted the manuscript. XZ and KQ revised the manuscript. XZ and YQR analyzed and interpreted the data. XZ and KQ and made substantial contributions to the conception of the work. YR and HH made substantial contributions to the design of the work and have revised the manuscript substantively. All authors contributed to the article and approved the submitted version.

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REVIEW
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Recurrent Intrahepatic Cholangiocarcinoma – Review

Yuki Bekki[1], *Dagny Von Ahrens*[1], *Hideo Takahashi*[2], *Myron Schwartz*[1] *and Ganesh Gunasekaran*[1,2*]

[1] Division of Liver Surgery, Recanati/Miller Transplantation Institute, The Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2] Department of Surgery, Mount Sinai South Nassau, Oceanside, NY, United States

Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver malignancy after hepatocellular carcinoma. While surgical resection with negative margin is the only curative treatment, ICC has very high rate of recurrence, up to 60-70% after curative resection. We reviewed the current data available on risk factors for ICC recurrence, recurrence pattern (location and timing), treatment options, and future directions. The risk factors for recurrence include elevated preoperative CA19-9, presence of liver cirrhosis, nodal metastasis, positive margins, and vascular invasion. Understanding different recurrence patterns, timing course, and risk factors for early recurrence is important to tailor postoperative surveillance and select treatment strategies including systemic or locoregional therapy. Re-resection can be considered for a selected patient population at experienced centers, and can yield long-term survival. ICC remains a dismal disease given the high likelihood of recurrence. Advances in our understanding of the genomic landscape of ICC are beginning to identify targetable alterations in ICC in subsets of patients that allow for personalized treatment.

Keywords: intrahepatic cholangiocarcinoma, recurrence, management, risk factors for recurrence, re-resection of the liver

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Alessandro Vitale,
University Hospital of Padua, Italy

Reviewed by:
David Fuks,
Assistance Publique Hopitaux De Paris, France
Jong Man Kim,
Sungkyunkwan University, South Korea

***Correspondence:**
Ganesh Gunasekaran
ganesh.gunasekaran@mountsinai.org

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INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver malignancy, comprising of 5-10% of all primary liver cancers (1). Likely due to increasing use of cross-sectional imaging, its incidence has been increasing in the US and worldwide in the past several decades (2–5). Despite advance in systemic treatment (6, 7), surgical resection with negative margins is the only curative treatment for ICC (8–13). However, even with successful resection combined with adjuvant systemic chemotherapy, 5-year survival has ranged between 25-43% (8, 14–17) due to the high rate of recurrence. While the median survival after recurrence is approximately 12 months (14, 16), there is increasing evidence that aggressive multimodality treatment including re-resection may be prolong survival in selected patient populations (15, 16, 18).

Given the high recurrence rate, we aim to summarize the risk factors for recurrence, recurrence patterns, treatment options, and future directions in recurrent ICC management in this review.

RISK FACTORS FOR RECURRENCE

Due to the heterogeneity of patients and tumor characteristics, management of ICC has to be tailored to the individual patient, including, for example, decisions about whether to employ adjuvant and/or neoadjuvant therapy (19, 20). Risk factors for recurrence in ICC have been extensively reported in the literature and include patient, histological, and treatment factors (21–24). The presence of underlying liver disease such as primary sclerosing cholangitis (PSC), viral hepatitis, and cirrhosis (21, 23) is a significant risk factor for both initial ICC incidence (25–27), and for increased recurrence after resection. Additionally, the presence of underlying liver disease can limit the ability to perform major resection which is often necessary in ICC to achieve oncologically optimal results (18). Elevated pretreatment carbohydrate antigen 19-9 is a marker of tumor aggressiveness and one of major risk factors for recurrence (28, 29).

Tumor-related risk factors include both gross characteristics like tumor size and number of lesions that are identifiable on imaging, and surgical margin status (30–33), vascular invasion (24, 29, 33) and regional nodal metastases (17, 24, 28, 29, 34) which are only identified histologically after surgery. Several nomograms have been reported to enable estimation of risk of recurrence based on tumor and patient risk factors (24, 29, 34).

Although recurrence risk is dependent on the treatment strategy, there are some controversies in this area.

Routine Lymphadenectomy

While nodal metastasis is a major risk factor for recurrence, the role of routine lymphadenectomy remains controversial in ICC management. The American Joint Committee on Cancer (AJCC) recommends a lymphadenectomy with a minimum retrieval of 6 lymph nodes for ICC (35), since microscopic nodal metastases have been demonstrated in more than 40% of patients (17). However, given the complex pattern of lymphatic flow from the liver, complete regional lymphadenectomy is challenging (36). In a meta-analysis performed by Zhou and colleagues, lymphadenectomy during resection of ICC did not alter patient survival (37). In a review of data from the Surveillance, Epidemiology, and End Results (SEER) database (38), Kizy et al. found similar median survival for patients with nodal metastasis treated with surgical resection or with chemotherapy alone.

On the other hand, Altman and colleagues reported a positive impact of lymphadenectomy in another SEER database study. While systemic chemotherapy was associated with improved survival after resection in patients with nodal metastasis, patients who did not undergo lymphadenectomy were significantly less-likely to receive adjuvant chemotherapy (39). An international multi-institutional study found that patients with nodal metastasis who had ≥ three lymph nodes resected had an improved survival compared with patients with fewer than three nodes removed, suggesting a therapeutic effect of lymphadenectomy; the number of lymph nodes resected did not correlate with outcome in patients without nodal metastasis (40). Given the rather low sensitivity of preoperative cross-sectional imaging to diagnose lymph node metastasis, routine lymphadenectomy has been advocated for staging as well as possible therapeutic effect (41). Despite the AJCC recommendation, the performance and extent of lymphadenectomy during resection of ICC remain a topic of debate.

Minimally Invasive Liver Resection

A recent retrospective study from a single institution used propensity score matching to demonstrate improved intraoperative and short-term outcomes, including number of nodes retrieved and depth of resection margin, with laparoscopic compared to open resection for ICC (42). Median disease-free survival (DFS) and overall survival (OS) were similar between the groups (DFS; 28 *vs*. 32 months, OS; 44 *vs*. 41 months). A recent meta-analysis of eight retrospective cohort studies confirmed the benefit of laparoscopic resection, showing a comparable number of nodes retrieved, a lower rate of positive margins, and improved DFS compared to open resetion (43).

On the other hand, a study based on the National Cancer Database (NCDB) found that patients who underwent laparoscopic resection more commonly had inadequate nodal sampling (laparoscopic 61% *vs*. open 39%; $p<0.001$) (44). The majority of studies advocating a minimally-invasive approach are single institution, retrospective studies and are thus highly heterogeneous and prone to selection bias (45, 46). At this point we can safely conclude that a minimallyinvasive approach is safe and feasible for selected patient populations at experienced centers.

Routine Systemic Chemotherapy

The use of adjuvant chemotherapy after resection of ICC has long been controversial, as results of trials have been mixed (47). The BILCAP trial, reported in 2019, demonstrated improved survival with adjuvant oral capecitabine therapy in a protocol-specified sensitivity analysis for a population comprising patients with a mix of intra- and extrahepatic cholangiocarcinoma and gallbladder cancer, but failed to meet its primary endpoint of overall survival in the intention-to-treat analysis (7). After gemcitabine plus cisplatin was established as first-line treatment for advanced biliary tract cancer based on the ABC-02 trial (6), gemcitabine plus oxaliplatin (GEMOX) was studied in the adjuvant setting in the PRODIGE 12-ACCORD 18 trial, and the regimen failed to demonstrate benefit after resection of biliary tract cancer (48).

Although the routine use of adjuvant chemotherapy remains controversial, it is commonly employed in patients where pathology reveals high-risk features including positive lymph nodes and/or positive margins (18, 24, 29, 34, 49, 50).

While there have been no randomized trials of neoadjuvant systemic therapy in ICC, several retrospective studies have been reported, especially in the setting of initially unresectable tumors. A multicenter retrospective analysis demonstrated comparable OS and DFS between patients who did or did not receive neoadjuvant chemotherapy despite the fact that the patients who received neoadjuvant therapy initially had more advanced disease (20). Two retrospective studies document the potential for neoadjuvant chemotherapy to downstage initially unresectable tumors to where resection becomes feasible (51, 52). Future studies of neoadjuvant therapy in ICC will be helpful, though conducting prospective trials in resectable ICC

has been challenging due to the low incidence and the heterogeneity of the disease.

RECURRENCE PATTERN

The high recurrence risk and poor prognosis of ICC is in large part the result of the disease only being discovered when it is relatively advanced locally; tumors are commonly large, and achieving complete resection is often technically challenging. Recurrence of ICC after curative surgical resection can occur at the resection margin, an intrahepatic site away from the margin, and/or extrahepatic organs; each manifestation has unique biology and patterns of progression. Furthermore, the timing of recurrence is also variable (53). Understanding different recurrence patterns, timing course and risk factors for early recurrence is important to tailor postoperative surveillance and to select treatment strategies including adjuvant therapy.

Recurrence Location/Organ

A multi-institutional study of 920 patients with ICC found that 607 (66.0%) patients developed recurrence following curative resection. One hundred forty five patients (23.9%) recurred at the resection margin, 178 (29.3%) recurred intrahepatically away from the margin, 90 (14.8%) had extrahepatic-only recurrence, and 194 (32.0%) had both intra-and extrahepatic recurrence. Major extrahepatic recurrence sites include lungs, lymph nodes, peritoneum, bone, and adrenal. The different recurrence patterns had different time courses: intrahepatic margin recurrence and extrahepatic-only recurrence were commonly observed within 6 months, while intrahepatic recurrence away from the margin occurred gradually within 2 years (54).

Recurrence Timing

The majority of ICC recurrence appears within two years of resection, and this is commonly defined as early recurrence (22, 23). Studies have demonstrated that recurrence patterns, risk factors, and outcomes differ significantly between patients with early *vs*. late recurrence. Not surprisingly, early recurrence is associated with worse prognosis (23). Tsilimigras et al. defined very early recurrence (VER) as recurrence within 6 months from initial resection based on distinct clinical features and more aggressive behavior noted in this group (21). Approximately one-quarter of patients with ICC in their series had VER, and their survival was dismal compared to those without VER (5-year OS 8.9% *vs*. 49.8%; p<0.001).

TREATMENT OF RECURRENCE

Although management of recurrent ICC is challenging and systemic therapy remains the cornerstone similar to patients who present primarily with advanced disease, several studies have reported benefit of incorporating aggressive locoregional treatment of recurrent disease compared to systemic therapy alone (15, 53).

Re-Resection

The majority of ICC recurs in the liver, and re-resection in selected patients is associated with long-term survival (14, 22, 23, 55–57). A multi-institutional study of 400 patients with ICC recurrence demonstrated that those who underwent re-resection had a median survival of 26.1 months, compared to 9.6 months for nonsurgical locoregional treatment and 16.8 months for systemic chemotherapy (55). Another recent multi-institutional study of 113 patients who underwent re-resection for recurrent ICC demonstrated median survival of 65.2 months (58). While 156 patients who underwent repeated exploration for recurrent ICC were included in their study, 43 patients (27.6%) did not undergo re-resection.

Repeat liver resection for recurrent ICC is often challenging since initial ICC resections are commonly major resections, often with concomitant vascular/biliary resection and reconstruction, and with lymphadenectomy around the hepatoduodenal ligament (59). Patients selected for re-resection, in addition to a technically favorable situation, typically have had a long disease-free interval (often greater than two years), less-advanced initial stage, negative lymph nodes, and no extrahepatic disease (59, 60). There have been many single institution studies from around the world that have reported survival benefit of re-resection, and without question there are long-term disease-free survivors. However, the obvious selection bias inherent in operative candidates makes valid statistical comparison of re-resection with other treatment modalities impossible (14, 16, 56, 59–62).

Locoregional Treatment

The use of locoregional treatments including thermal ablation (15), stereotactic body radiation therapy (SBRT) (63, 64), transarterial chemoembolization (TACE) and intraarterial yttrium-90 radiotherapy (16, 65), has been reported with varying degrees of success (66), and this remains an area of active investigation. **Table 1** summarizes the treatment modalities and corresponding outcomes for recurrent ICC (14, 55, 56, 58, 61, 63, 67–73). Zhang et al. reported comparable outcomes between thermal ablation group and re-resection group for recurrent ICC (median OS: 21.3 and 20.3 months, respectively). However, patients with recurrent tumor > 3cm demonstrated a higher OS rate in the re-resection group than those in the ablation group (67). Another single center retrospective study also identified a tumor size (> 2cm) as a risk factor for poor survival after thermal ablation for recurrent ICC (68).

TACE is another option with reasonable efficacy for unresectable recurrent ICC. A retrospective study of 275 patients with recurrent ICC included 183 patients who underwent TACE and 92 patients who underwent microwave ablation therapy. In their study, TACE provided longer survival after treatment than microwave coagulation therapy (median OS 26.9 *vs* 12.1 months). Interestingly, different prognostic factors for each treatment type were identified: the extent of tumor progression for TACE, and the etiologic subtype for microwave ablation therapy (71).

TABLE 1 | Treatment modality and survival after ICC recurrence.

Study	Treatment modality	No of patients	Size of tumor (cm)	Survival after recurrence (months)
Bartsch et al. (58)	re-resection	113	–	36.8
Si et al. (56)	re-resection	72	3	45.1
Zhang et al. (67)	re-resection	32	5	20.3
Yoh et al. (61)	re-resection	15	5	91.6
Zhang et al. (67)	ablation	77	–	21.3
Chu et al. (68)	ablation	40	1.5	26.6
Kim et al. (69)	ablation	20	1.5	27.4
Fu et al. (70)	ablation	12	3.2	30
Ge et al. (71)	TACE	183	6	26.9
Goerg et al. (72)	TACE	12	–	13.3*
Smart et al. (73)	radiation	66*	5.6	25*
Jung et al. (63)	radiation	30	–	13
Spolverato et al. (55)	chemotherapy	46	3	16.8
Park et al. (14)	chemotherapy	21	–	10

**Patients in both unresectable and recurrent ICC.*
Intrahepatic cholangiocarcinoma, ICC; Transarterial chemoembolization, TACE.

A meta-analysis of SBRT for unresectable or recurrent cholangiocarcinoma included 11 studies with 226 patients. The median OS was 13.6 months and 1-year local control rate was 78.6%, suggesting that SBRT was a feasible treatment option for those patients (64). These results are in line with the study by Jung et al. reporting the median OS of 13 months after SBRT for 30 patients with recurrent ICC (63). In order to apply higher dose of radiation towards tumors and reduce radiation related toxicity, proton radiation therapy have been introduced. Smart et al. demonstrated the efficacy of proton radiation therapy for 66 patients with unresectable or recurrent ICC with median OS of 25 months and 2-year local control of 84% (73). Even though radiation related toxicity can be a barrier to dose escalation, radiation therapy remains an effective local modality for recurrent ICC.

Although the level of evidence is limited due to the retrospective design and potential selection bias in these studies, locoregional treatment for recurrent ICC was associated with prolonged survival in patients with recurrent ICC (14–16, 22, 55, 59). With various locoregional treatment options available, comprehensive patient and tumor information is needed to stratify patients to select the treatment option including multimodal approach.

FUTURE DIRECTIONS

With recent technological advances in Next Generation Sequencing (NGS), genomic profiling of tumors has become significantly easier and more affordable. As has been demonstrated in other cancer types (74, 75), molecular analysis of tumors can help clinicians to tailor the treatment for advanced or recurrent ICC (76, 77). The incidence of actionable mutations in patients with ICC ranges from 30-70%, with the most common being IDH1 and FGFR-2 (12, 78, 79). Similar to pancreatic cancer, targeting other genomic alterations such as DNA damage repair genes, HER2 amplification or activation, and NTRK gene fusions can improve survival compared to conventional systemic chemotherapy alone (74).

Immunotherapy has revolutionized cancer treatment and is currently being studied in ICC (80, 81). Identification of DNA mismatch repair deficiency on biopsy or surgical specimens is now routine, and as with other tumor types, these patients have a high rate of response to checkpoint inhibitors. While several biomarkers of response to immunotherapy have been identified, such as tumor mutation burden, presence of tumor-infiltrating lymphocytes, or programmed death-ligand 1 expression status (combined positive score) (82, 83), the response rate remains low (12, 78), and checkpoint inhibitors are generally given together with cytotoxic chemotherapy. As with most cancers, identifying biomarkers or genetic signatures of ICC that predict response to therapy is an area of intense research and will be integral to establishing an effective, personalized approach.

CONCLUSIONS

ICC is the second most common primary liver malignancy with high risk of recurrence after curative resection. Risk factors for recurrence have been defined, and the majority of patients will have recurrent disease within 2 years of the initial resection. Prognosis after recurrence remains grim and treatment options beyond systemic treatment after recurrence are limited. While it can be technically challenging, repeat resection is a feasible and safe option for selected patients at experienced centers and can result in long-term survival. Other locoregional options such as thermal ablation, SBRT, TACE or intraarterial radioembolization increasingly being employed in conjunction with systemic therapy. Sequencing of tumor DNA is now routine in patients with ICC and can identify actionable mutations and genomic alterations that can help clinicians tailor treatment to manage this aggressive malignancy.

AUTHOR CONTRIBUTIONS

YB, DA, and HT drafted the manuscript MS and GG conceived the study and were in charge of overall direction and planning. All authors reviewed the results and approved the final version of the manuscript.

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A Novel Blood Index-Based Model to Predict Hepatitis B Virus-Associated Hepatocellular Carcinoma Recurrence After Curative Hepatectomy: Guidance on Adjuvant Transcatheter Arterial Chemoembolization Choice

Yiping Zou[1,2], *Zhihong Chen*[1,2], *Qi Lou*[1,3], *Hongwei Han*[1,3], *Yuanpeng Zhang*[1], *Zhenrong Chen*[1], *Zuyi Ma*[1,2], *Ning Shi*[1*] and *Haosheng Jin*[1,2,3*]

[1] Department of General Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China, [2] College of Medicine, Shantou University, Shantou, China, [3] The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Background: Postoperative recurrence is a significant obstacle in hepatocellular carcinoma (HCC) treatment. This study aimed to construct a blood index-based model to predict hepatitis B virus-associated HCC (HBV-HCC) recurrence after curative hepatectomy.

Methods: A total of 370 patients who received initially curative hepatectomy for HBV-HCC were included in this study. A novel blood index signature (BIS) was identified and systematically analyzed for its recurrence predictive value. Following this, multivariate Cox regression analysis was performed to build a blood index-based nomogram.

Results: A BIS based on the aminotransferase-to-platelet ratio index and a systemic inflammatory response index was used to construct a nomogram. The model showed good clinical applicability and reliability. Notably, the patients in the high recurrence risk group tended to benefit from adjuvant transcatheter arterial chemoembolization (TACE).

Conclusion: A reliable model was constructed to predict the HBV-HCC recurrence after curative hepatectomy. This model can guide the surgeons in selecting patients with high recurrence risk patients who may benefit from adjuvant TACE.

Keywords: hepatocellular carcinoma, blood index signature, nomogram, recurrence-free survival, adjuvant transcatheter arterial chemoembolization

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Sant'Orsola-Malpighi Polyclinic, Italy

***Correspondence:**
Haosheng Jin
kinghaos@126.com
Ning Shi
shining_doc@163.com

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INTRODUCTION

Hepatocellular carcinoma (HCC), the fourth common cause of cancer worldwide, causes more than 600,000 deaths annually. Hepatitis B virus (HBV) infection is the major HCC contributor worldwide (1, 2). Regarding HCC treatment, only curative resection allows patients with HCC to achieve long-term survival. However, the postoperative high recurrence rate is a significant obstacle in cancer management (3, 4). Even for patients with early-stage with small tumors, the 5-year recurrence rate after surgery is approximately 70% (5).

Currently, transcatheter arterial chemoembolization (TACE) is the standard mainstay of treatment for intermediate-stage HCC (6). Although several studies have reported on adjuvant therapeutic modalities, the role of adjuvant TACE in resectable HCC remains controversial (7–9), which can be attributed to the considerable heterogeneity of HCC. The adjuvant therapy may improve the survival benefits of high-risk patients; however, these benefits may be impaired in low-risk patients. Therefore, identifying novel biomarkers and constructing an accurate prediction model based on postoperative HCC recurrence provide physicians with more appropriate therapeutic options. For example, peripheral blood microRNAs were identified as prognostic predictors in patients with HCC who received TACE (10). The result showed that miR-21 and miR-122 were prognostic biomarkers in HCC patients treated with TACE and correlated with hypoxia-inducible factor-1α (HIF-1α) serum levels.

Obtaining the peripheral blood index is convenient and inexpensive. Previous studies have reported that blood indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), aminotransferase-to-platelet ratio index (APRI), aspartate aminotransferase-to-neutrophil ratio index (ANRI), systemic immune-inflammatory index (SII), systemic inflammatory response index (SIRI), fibrinogen-to-albumin ratio (FAR), fibrinogen-to-lymphocyte ratio (FLR), γ-glutamyl transpeptidase-to-platelet ratio (GPR), model for end-stage liver disease (MELD), Albumin-Bilirubin (ALBI) Grade, and prognostic nutritional index (PNI) reflect the HCC survival (11–20). Therefore, this study aimed to construct a novel blood index-based model that can accurately predict HBV-associated HCC (HBV-HCC) recurrence.

METHODS

Study Population

The data of 370 patients pathologically diagnosed with HBV-HCC who received curative hepatectomy as the first line of treatment were retrospectively collected at the Guangdong Provincial People's Hospital from January 2013 to December 2019. The exclusion criteria included the following: 1) patients younger than 18 years; 2) patients without the negative surgical margin; 3) patients who underwent neoadjuvant downstage therapy; 4) patients with recurrent HCC; 5) patients with preoperative incomplete data on blood indices; and 6) patients with a follow-up period of less than 6 months. This study was approved by the ethics committee of Guangdong Provincial People's Hospital (KYZ202132501) and performed following the Declaration of Helsinki.

Management Protocol

Preoperative blood indices and clinicopathological data within 7 days before surgery were collected retrospectively from the electronic medical record system. Contrast-enhanced CT or contrast-enhanced MRI combined with serum alpha-fetoprotein (AFP) was performed during the first month of the first-year follow-up and every 3 months after that to detect early recurrence. Following this, the patients were recommended to undergo imaging examinations every 6 months for 1 year after surgery. Additionally, imaging examinations were performed if patients had chief complaints such as abdominal pain.

Moreover, a multidisciplinary treatment discussion was conducted for every patient before hepatectomy. As the commonly used adjuvant management, all patients were recommended to receive adjuvant TACE 1–2 months after surgery. The highly selective conventional TACE was used for this adjuvant management.

Recurrence-free survival (RFS) was defined as the time from curative hepatectomy to tumor recurrence at any site. The overall survival (OS) was defined as the time from the curative hepatectomy to death, due to any cause, or last contact.

Statistical Analyses

Continuous variables were presented as the mean and SD, whereas categorical variables were expressed as frequency and percentage. Univariate Cox regression analysis was performed to estimate the indices associated with RFS, and stepwise multivariate Cox regression analysis was performed to build a blood index signature (BIS). The following formula was used to calculate the BIS: $H0 * Exp[\Sigma(\beta i \times xi)]$. Furthermore, the univariate and multivariate Cox regression analyses were used to assess the independence of novel signature in evaluating RFS based on clinicopathological variables and construct a predictive nomogram. The area under the receiver operating characteristic (ROC) curve was used to evaluate the predictive performance. Calibration curves were used to compare the association between the actual outcomes and predicted probabilities. The best cutoff value for risk stratification was calculated using the X-tile software (Yale School of Medicine, USA). Additionally, the Kaplan–Meier survival curves with log-rang text and subgroup Cox regression analyses were plotted to compare differences in RFS or OS. Decision curve analysis (DCA) was used to evaluate the clinical applicability of the nomogram.

Statistical analyses in this study were performed using the R software version 4.0.5. Unless otherwise stipulated, a two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The clinicopathological characteristics of the study's cohort are summarized in **Table 1**. The patients were predominantly male,

TABLE 1 | Baseline patient demographics and preoperative characteristics.

Variables	Group (370)
Age (years)	54.22 ± 11.39
Size (cm)	5.44 ± 3.46
Gender	
Female	45 (12.2)
Male	325 (87.8)
Ki67	
<20%	206 (55.7)
≥20%	164 (44.3)
Multiple tumors	
No	319 (86.2)
Yes	51 (13.8)
Capsule invasion	
No	320 (86.5)
Yes	50 (13.5)
Grade	
I/II	172 (46.5)
III/IV	198 (53.5)
MVI	
No	261 (70.5)
Yes	109 (29.5)
Adjunct TACE	
No	244 (65.9)
Yes	126 (34.1)
AFP (ng/ml)	
<20	171 (46.2)
≥20	199 (53.8)
Laparoscopic surgery	
No	229 (61.9)
Yes	141 (38.1)
Child–Pugh classification	
Class A	343 (92.7)
Class B	27 (7.3)
NLR	2.11 ± 1.09
PLR	116.47 ± 66.09
MLR	0.33 ± 0.16
FAR	0.12 ± 0.49
GPR	0.51 ± 0.62
APRI	0.82 ± 0.78
PNI	37.94 ± 5.01
ALBI	−2.44 ± 0.44
FLR	2.78 ± 10.86
SII	415.48 ± 321.12
SIRI	1.17 ± 0.88
ANRI	15.79 ± 15.38
MELD	5.92 ± 0.35

MVI, microvascular invasion; TACE, transcatheter arterial chemoembolization; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; APRI, aminotransferase-to-platelet ratio index; ANRI, aspartate aminotransferase-to-neutrophil ratio index; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; FAR, fibrinogen-to-albumin ratio; FLR, fibrinogen-to-lymphocyte ratio; GPR, γ-glutamyl transpeptidase-to-platelet ratio; MELD, end-stage liver disease; ALBI, Albumin-Bilirubin Grade; PNI, prognostic nutritional index.

with a solitary tumor, without capsule and microvascular invasions (MVIs), and had well-reserved liver function (Child–Pugh class A). The average age of the cohort is 54.22 years. A total of 141 (38.1%) patients underwent laparoscopic surgery, and 126 (34.1%) received adjuvant TACE. The average tumor size is 5.44 cm. A total of 164 (44.3%) patients with Ki67 ≥ 20% and 172 (46.5%) patients with grade III/IV tumor differentiation were observed. Notably, 171 (46.2%) patients showed negative AFP (AFP < 20 ng/ml) result.

Construction of the Novel Blood Index Signature

Univariate Cox analyses were performed to filter blood indices associated with the RFS of HBV-HCC. Blood indices significantly associated with RFS were further analyzed using stepwise multivariate COX regression. Subsequent stepwise elimination of the blood indices resulted in APRI and SIRI as significant predictors for the RFS of HBV-HCC (**Table 2**). The following formula was used to calculate the BIS: 0.447 * Exp (0.340552 * APRI + 0.447854 * SIRI).

Blood Index Signature and Clinicopathological Parameters

Univariate Cox regression analysis was used to identify the predicted values of RFS in BIS and clinicopathological parameters. Furthermore, the association between RFS and Ki67, size, tumor number, AFP, MVI, and BIS score was analyzed using (**Figure 1A**) multivariate regression analyses, wherein Ki67, size, MVI, and BIS were found to be independent prognostic predictors of RFS (**Figure 1B**). Moreover, the BIS achieved the highest AUC value as compared with the other clinicopathological parameters (**Figure 1C**). Following this, BIS levels in different clinicopathological subgroups were assessed. The results indicated BIS levels were significantly higher in patients with AFP positive values, grade III/IV, MVI, and tumor size ≥5 cm ($p < 0.001$) (**Figures 2A–F**).

Construction of a Nomogram to Predict the Recurrence-Free Survival of Hepatocellular Carcinoma

In multivariate Cox regression analysis, tumor number with $p < 0.1$ and hazard ratio (HR) = 1.416 (95% CI = 0.947–2.119) was screened for constructing the model owing to its greater clinical significance. A nomogram was constructed based on Ki67, tumor size, tumor number, MVI, and BIS (**Figure 3A**), with each clinicopathological characteristic corresponding to a specific point. The sum of the values was represented on the total points axis, whereas the probabilities of 0.5-, 1-, and 2-year RFS were represented on the corresponding axis.

Performance and Clinical Usefulness of the Nomogram

The AUC values of ROC of the nomogram were 0.778, 0.752, and 0.706 in 0.5-, 1-, and 2-year RFS prediction, respectively (**Figure 3B**). The calibration plots for the probabilities of 0.5-, 1-, and 2-year RFS demonstrated positive concurrences between the nomogram predictions and actual observations (**Figures 3C–E**). The study cohort was divided into high and low recurrence risk groups according to an optimal cutoff value (28.7) determined using the X-tile software. As shown in **Figures 4A, B**, patients in the low recurrence risk group showed better RFS ($p = 5.766e{-}13$) and OS ($p = 2.998e{-}15$) than those in the high recurrence risk group. The nomogram showed a better net benefit than that of MVI and tumor size within a wide range of threshold probability (**Figure 4C**).

TABLE 2 | Cox regression of blood indexes for the RFS of HBV-HCC patients.

Variables	Univariate Cox		Stepwise multivariable Cox		
	HR (95% CI)	*p*-Value	HR (95% CI)	Coef	*p*-Value
NLR	1.374 (1.207–1.564)	<0.001			
PLR	1.002 (0.999–1.004)	0.090			
MLR	3.862 (1.720–8.673)	0.001			
FAR	0.935 (0.584–1.496)	0.779			
GPR	1.188 (0.971–1.455)	0.095			
APRI	1.334 (1.118–1.592)	0.001	1.406 (1.201–1.646)	0.340552	<0.001
PNI	0.977 (0.946–1.008)	0.138			
ALBI	1.336 (0.945–1.908)	0.112			
FLR	0.999 (0.982–1.016)	0.922			
SII	1.001 (1.000–1.001)	<0.001			
SIRI	1.507 (1.292–1.757)	<0.001	1.565 (1.346–1.820)	0.447854	<0.001
ANRI	1.010 (1.001–1.019)	0.029			
MELD	0.957 (0.609–1.504)	0.848			

RFS, recurrence-free survival; HBV-HCC, hepatitis B virus-associated hepatocellular carcinoma; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; APRI, aminotransferase-to-platelet ratio index; ANRI, aspartate aminotransferase-to-neutrophil ratio index; SII, systemic immune-inflammatory index, SIRI, systemic inflammatory response index, FAR, fibrinogen-to-albumin ratio; FLR, fibrinogen-to-lymphocyte ratio; GPR, γ-glutamyl transpeptidase-to-platelet ratio; MELD, end-stage liver disease; ALBI, Albumin-Bilirubin Grade; PNI, prognostic nutritional index.

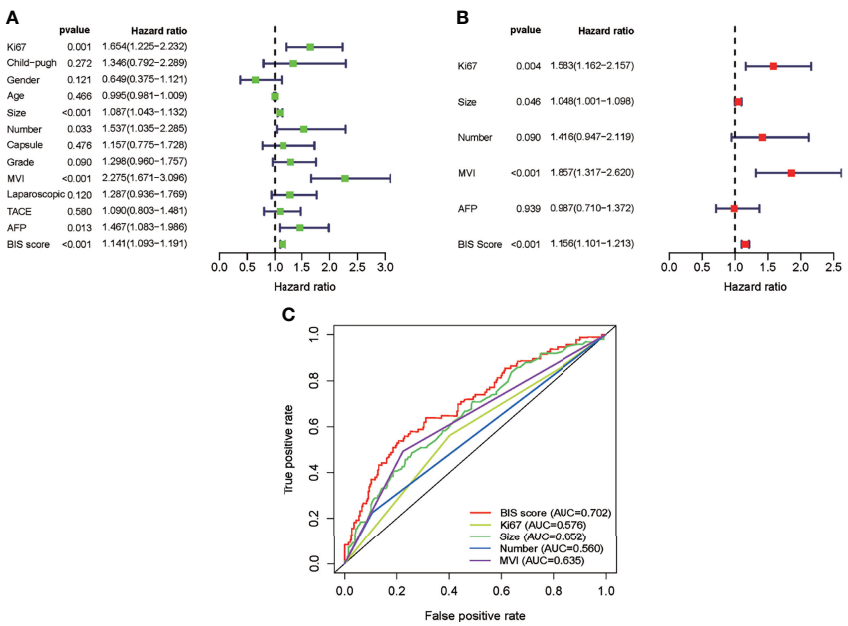

FIGURE 1 | **(A)** Univariate Cox analysis of the blood index signature (BIS) and other clinicopathological characteristics. **(B)** Multivariate Cox analysis of BIS and other clinicopathological characteristics. **(C)** Receiver operating characteristic (ROC) of BIS score and other clinicopathological characteristics.

Adjuvant Transcatheter Arterial Chemoembolization Efficiency in Different Subgroups

Cox regression analysis was used to determine the efficiency of adjuvant TACE in different subgroups. Patients in the low recurrence risk group, who received adjuvant TACE, showed no improvement in RFS (HR = 1.165, 95% CI = 0.786–1.727, p = 0.447) and OS (HR = 1.109, 95% CI = 0.532–2.310, p = 0.780). However, patients in high recurrence risk group showed improvement in OS (HR = 0.527, 95% CI = 0.281–0.991, p = 0.047) but not in RFS (HR = 0.862, 95% CI = 0.525–1.414, p = 0.556) (**Figure 4D**). Furthermore, the Kaplan–Meier analysis was performed to evaluate the RFS and OS of patients with or without adjuvant TACE in high recurrence and low recurrence risk groups. In the low recurrence risk group, patients who underwent adjuvant TACE showed no benefits regarding RFS (p = 0.4456) and OS (p = 0.7842) (**Figures 5A, B**). Although the patients in the high recurrence risk group who received adjuvant TACE showed no benefits regarding RFS (p = 0.5727), the OS (p = 0.04516) of those who underwent TACE was more beneficial than of those

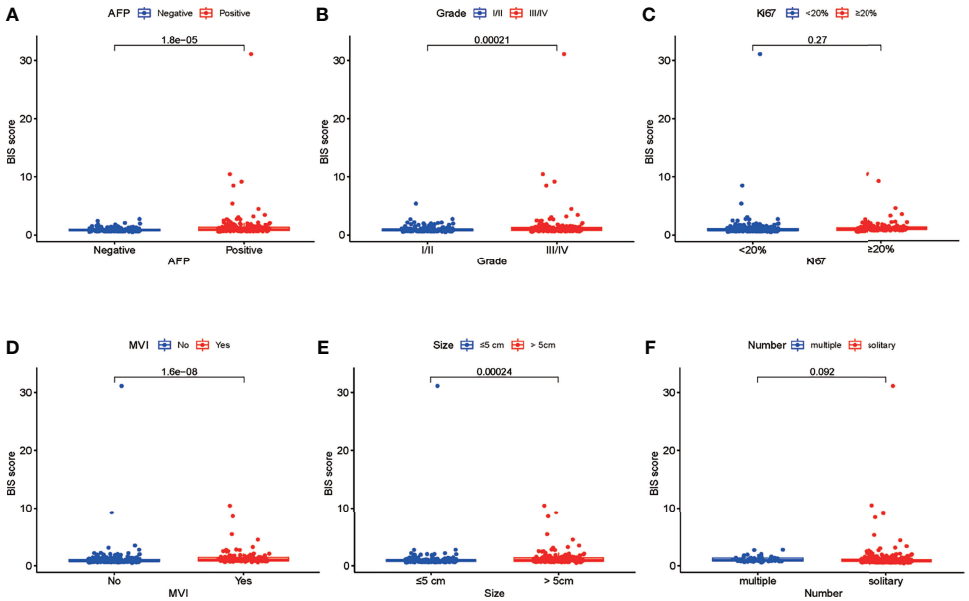

FIGURE 2 | **(A–F)** Differences in the blood index signature (BIS) score between patients with different subgroups of serum alpha-fetoprotein (AFP), tumor grade, Ki67, microvascular invasion (MVI), tumor size, and tumor number.

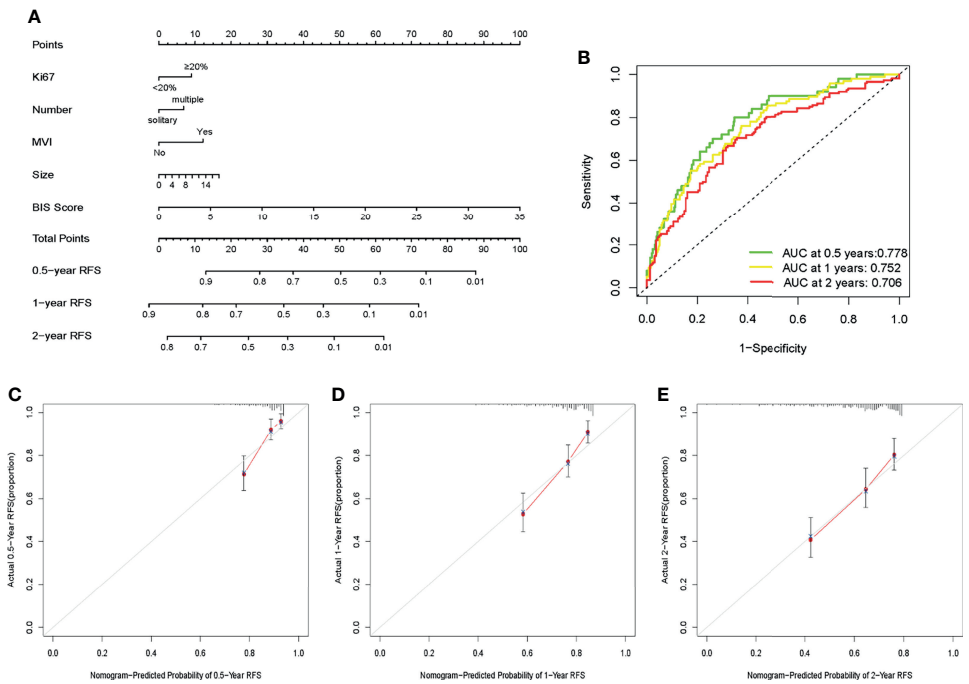

FIGURE 3 | **(A)** Nomogram for predicting the recurrence-free survival (RFS) in patients with hepatitis B virus-associated hepatocellular carcinoma (HBV-HCC). **(B)** Receiver operating characteristic (ROC) curves of the nomogram to predict 0.5-, 1-, and 2-year recurrence-free survival (RFS). **(C–E)** Calibration plots of the nomogram to predict 0.5-, 1-, and 2-year RFS.

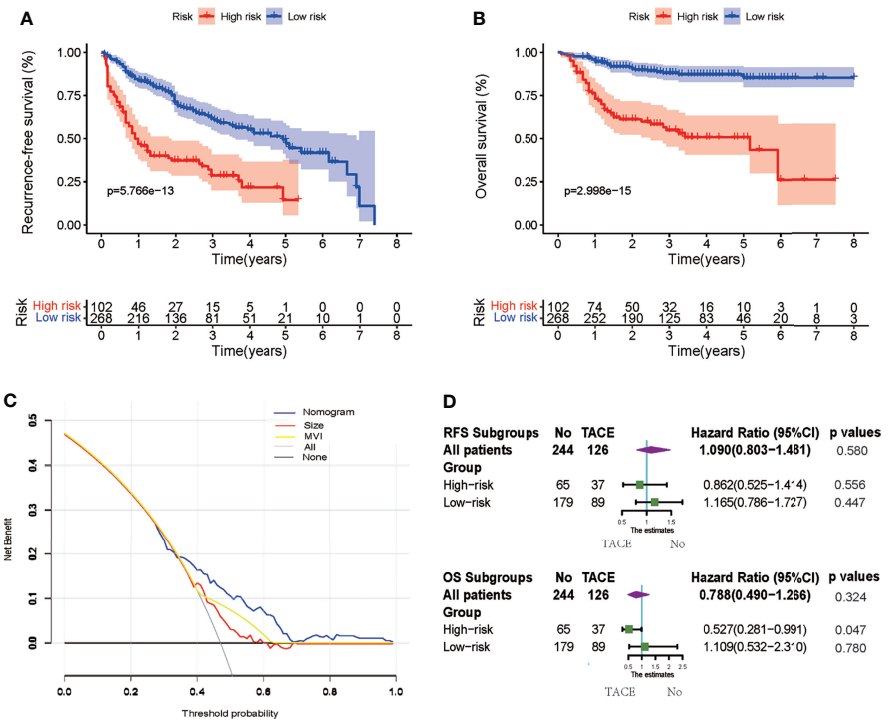

FIGURE 4 | **(A, B)** Kaplan–Meier survival curves to estimate recurrence-free survival (RFS) and overall survival (OS) stratified by risk subgroups. **(C)** Decision curve analysis (DCA) showing the net benefit of the nomogram, microvascular invasion (MVI), and tumor size. **(D)** Subgroup Cox analysis demonstrating the impact of adjuvant transcatheter arterial chemoembolization (TACE) on RFS and OS in different risk subgroups.

without adjuvant TACE (**Figures 5C, D**). Considering the short-term recurrence rate in the high recurrence risk group, the 3-month recurrence rate was significantly lower in patients who underwent adjuvant TACE (p = 0.02557) (**Figure 5E**). Although the 6-month RFS showed no significant difference, a better and beneficial RFS trend was observed in patients who underwent adjuvant TACE (**Figure 5F**).

DISCUSSION

In the retrospective study, we constructed an accurate and user-friendly model based on BIS, MVI, Ki67, tumor size, and tumor number to predict the recurrence of HBV-HCC after curative hepatectomy. This model showed good efficacy in discriminating between high and low recurrence risk groups. Notable, adjuvant TACE for patients in the high recurrence risk group showed better OS.

The high rate of recurrence after curative resection remains a great challenge in HCC treatment (21). Previous studies have confirmed that MVI is a critical determinant of the early recurrence of HCC (22, 23). Moreover, Bai et al. demonstrated that Ki67 expression was positively correlated with the increased risk of death and recurrence (24). Additionally, various studies have indicated that systemic inflammation plays a central role in tumor promotion and progression, thereby promoting HCC recurrence postoperatively (25, 26). APRI, a strong indicator of liver inflammation and necrosis in cirrhotic liver, was considered as a risk factor for HCC recurrence postoperatively (27). SIRI was also considered as a reliable marker for prognostic prediction in patients with HCC, which correlated with liver function (28). This study comprehensively analyzed 13 immune indices and confirmed that APRI and SIRI are independent prognostic indices for the recurrence of HBV-HCC after curative hepatectomy. Therefore, an IBS signature was constructed based on APRI and SIRI, which were highly accurate and independent prognostic predictors for recurrence.

However, as adjuvant TACE does not benefit all patients, it is vital to define prognostic categories and recommend TACE to patients who may benefit from this treatment (8, 29). This study provides a novel grouping method based on BIS, which screens patients who benefit from adjuvant TACE. Patients in the low recurrence risk who received adjuvant TACE showed no improvement in RFS and OS. However, patients in the high recurrence risk group who underwent adjuvant TACE showed improved and significantly longer OS but showed no improvement in RFS. The poor OS could be attributed to the high short-term recurrence rate in patients who did not receive TACE. Previous studies have also indicated that early recurrence is associated with worse postoperative survival among patients with HBV-HCC (30–32).

Currently, immunotherapy, especially immune-checkpoint inhibitor therapies, has been successful in treating advanced

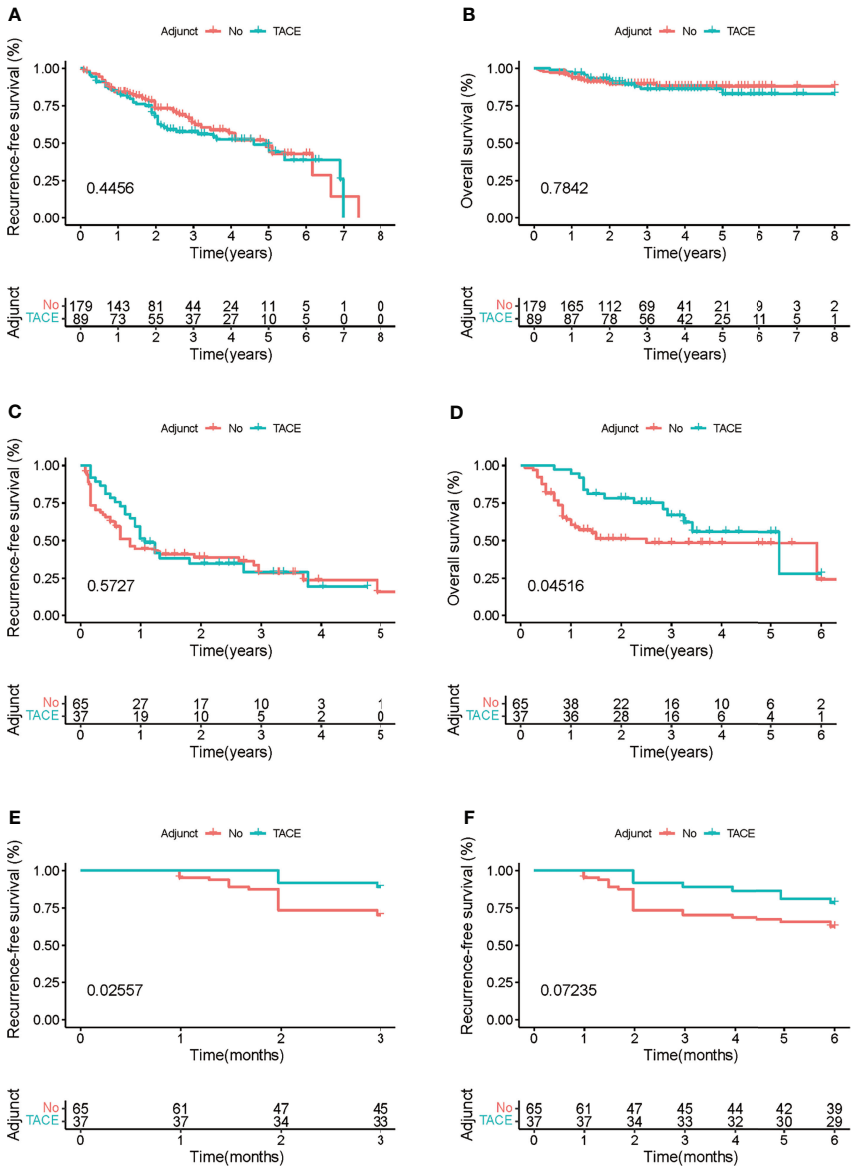

FIGURE 5 | **(A, B)** Kaplan–Meier survival curves of the impact of adjuvant transcatheter arterial chemoembolization (TACE) on recurrence-free survival (RFS) and overall survival (OS) in patients with low recurrence risk. **(C, D)** Kaplan–Meier survival curves of the impact of adjuvant TACE on RFS and OS in patients with high recurrence risk. **(E, F)** Kaplan–Meier survival curves of the impact of adjuvant TACE on RFS and OS in patients with high recurrence risk within 3 and 6 months.

HCC (33, 34). Combining locoregional therapy approaches such as TACE with immunotherapy is an interesting treatment plan, which may provide better results (35). The BIS model can divide patients into high and low recurrence risk groups, which can be used to filter patients for receiving adjuvant therapy.

However, this study still has several limitations. First, this is a retrospective single-center study, which introduces potential selection bias and has relatively limited evidence. However, the strict exclusion criteria in this study reduced the bias. Second, a validation cohort could not be set up because of the limited case number from a single institution. A validation cohort with a large population can be used in future studies. Third, the efficacy of adjuvant TACE requires further verification using a prospective randomized controlled study, which can help in constructing a more convincing prognostic model for clinical guidance.

CONCLUSION

In summary, this study identified and constructed a blood index-based model to predict the HBV-HCC recurrence after curative hepatectomy. This novel model is an effective tool for identifying patients with a high risk of recurrence and who may benefit from adjuvant TACE.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Guangdong Provincial People's Hospital (KYZ202132501). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YIZ: collection acquisition, data analyses, and manuscript writing. ZHC, QL, and HH: analyses and interpretation. YUZ, ZRC, and ZM: data acquisition. NS and HJ: project development and critical revisions.

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Prediction of Microvascular Invasion and Its M2 Classification in Hepatocellular Carcinoma Based on Nomogram Analyses

Shengsen Chen[1†], Chao Wang[2†], Yuwei Gu[3†], Rongwei Ruan[1], Jiangping Yu[1] and Shi Wang[1]*

[1] Department of Endoscopy, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, China, [2] Department of Emergency, Huashan Hospital affiliated to Fudan University, Shanghai, China, [3] Department of Rehabilitation Medicine, Huashan Hospital affiliated to Fudan University, Shanghai, China

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****Correspondence:***
Shi Wang
wangshi@zjcc.org.cn

[†]These authors have contributed equally to this work

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Background and Aims: As a key pathological factor, microvascular invasion (MVI), especially its M2 grade, greatly affects the prognosis of liver cancer patients. Accurate preoperative prediction of MVI and its M2 classification can help clinicians to make the best treatment decision. Therefore, we aimed to establish effective nomograms to predict MVI and its M2 grade.

Methods: A total of 111 patients who underwent radical resection of hepatocellular carcinoma (HCC) from January 2017 to December 2019 were retrospectively collected. We utilized logistic regression and least absolute shrinkage and selection operator (LASSO) regression to identify the independent predictive factors of MVI and its M2 classification. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated to select the potential predictive factors from the results of LASSO and logistic regression. Nomograms for predicting MVI and its M2 grade were then developed by incorporating these factors. Area under the curve (AUC), calibration curve, and decision curve analysis (DCA) were respectively used to evaluate the efficacy, accuracy, and clinical utility of the nomograms.

Results: Combined with the results of LASSO regression, logistic regression, and IDI and NRI analyses, we founded that clinical tumor-node-metastasis (TNM) stage, tumor size, Edmondson–Steiner classification, α-fetoprotein (AFP), tumor capsule, tumor margin, and tumor number were independent risk factors for MVI. Among the MVI-positive patients, only clinical TNM stage, tumor capsule, tumor margin, and tumor number were highly correlated with M2 grade. The nomograms established by incorporating the above variables had a good performance in predicting MVI (AUC_{MVI} = 0.926) and its M2 classification (AUC_{M2} = 0.803). The calibration curve confirmed that predictions and actual observations were in good agreement. Significant clinical utility of our nomograms was demonstrated by DCA.

Conclusions: The nomograms of this study make it possible to do individualized predictions of MVI and its M2 classification, which may help us select an appropriate treatment plan.

Keywords: hepatocellular carcinoma, microvascular invasion (MVI), M2 classification, prediction model, nomogram

INTRODUCTION

Primary liver cancer is one of the most common cancers worldwide and globally ranks fifth and fourth in morbidity and mortality, respectively (1). In China, liver cancer was reported as the fourth most common cancer in 2015, and its mortality ranked second among malignant tumors (2), with approximately 466,100 new cases and 422,000 deaths (3). As the most common type of liver cancer, hepatocellular carcinoma (HCC) has high invasiveness, and its 5-year recurrence rate after surgery is nearly 70% (4, 5), which results in a poor prognosis (6). Despite the diagnosis and treatment of HCC having been greatly improved, recurrence within 5 years after operation still remains a huge challenge (7). Microvascular invasion (MVI), an indicator (only diagnosed by histopathological examination) of HCC aggressive behavior (8), is defined as the cancer cell nest appearing in vessels lined with endothelium under microscopy (9, 10). When MVI is present, tumor cells can spread and metastasize in the liver, forming portal vein tumor thrombi or multiple lesions or distant metastasis (11). So MVI is considered as a critical pathological factor correlated with tumor recurrence and survival (12) and has been used as a prognostic reference index in the treatment options for both primary and recurrent HCC (13, 14). In resected HCC specimens, MVI was detected in approximately 7.8% to 74.4% of cases (15), and the MVI detection rate in early HCC varied greatly from 12.4% to 37.3% (16).

Recently, the three-tiered MVI grading system (MVI-TTG) has been proposed and it classifies the specimens as M0 (no MVI), M1 (1–5 sites of MVI and located at ≤1 cm away from the tumor-adjacent liver tissue), and M2 (>5 MVI sites or at >1 cm away from the tumor-adjacent liver tissue) (17). The MVI-TTG scheme is simple and clear, is easy to implement, and can stratify HCC patients in different risks for recurrence and survival (18). In the presence of MVI, HCC patients with M2 classification showed a worse prognosis after radical resection than those with M1 classification. Moreover, the M2 grade of MVI is a high-risk factor for postoperative residual cancer recurrence and intrahepatic metastasis (18). Therefore, we should pay attention not only to the presence or absence of MVI but also to its M2 classification.

If HCC patients who require liver resection are at high risk of MVI, it is recommended to widen the surgical margin to eradicate MVI and improve clinical prognosis (19). When MVI is present and classified as M2 grade, more intense comprehensive treatment such as adjuvant transarterial chemoembolization (TACE) may need to be taken to prevent HCC postoperative recurrence and metastasis (20). Given that MVI, especially its M2 grade, is the poor prognostic factor of HCC (18), there is an urgent need to build effective and accurate prediction models that can predict MVI and its M2 classification to optimize the management of patients (21). A few studies have built and validated some nomograms for MVI prediction, but the inclusion criteria of HCC patients were heterogeneous and so were the clinical characteristics of selected patients in these studies (22). Additionally, the study on the risk prediction of M2 classification in the presence of MVI is still rare currently.

Therefore, in this study, we aimed to determine the effective predictors of MVI and its M2 classification and use these factors to establish corresponding nomograms, which could aid clinicians to select appropriate therapeutic strategies for MVI-positive HCC patients and make the follow-up after curative treatment more targeted.

METHODS

Patients and Study Design

We retrospectively collected a total of 111 HCC patients with liver resection from January 2017 to December 2019. The criteria for the exclusion of patients were as follows: 1) abdominal contrast-enhanced CT and blood index tests were performed more than 1 week before surgery; 2) the surgical margin was not confirmed to be R0 defined in a previous report (23); 3) patients underwent hepatectomy more than one time; 4) patients received radiofrequency ablation (RFA), TACE, neoadjuvant chemotherapy, and/or radiotherapy before surgery; 5) patients who have a history of other malignant tumors; 6) MVI status was not evaluated by histopathological examination; 7) HCCs with macrovascular or extrahepatic invasion; and 8) incomplete clinical data. The flowchart of the patient selection is summarized in **Figure 1**.

Clinical Variables and Pathological Characteristics

Basic information on admission such as age, sex, symptoms at diagnosis, and some laboratory indicators was collected including blood routine test, liver and kidney function, hepatitis B tests, and tumor markers. Besides, data of tumor size, liver cirrhosis, number of HCC lesions, tumor location, tumor margin, and tumor capsule were extracted from the results of preoperative abdominal contrast-enhanced CT scans. The cardiopulmonary function was also evaluated by cardiac ultrasound and pulmonary function test to make sure the patients can tolerate the operation. The postoperative tissue specimens were further assessed by pathological examination to confirm the presence or absence of MVI. As described above, patients with positive MVI were classified into M1 and M2

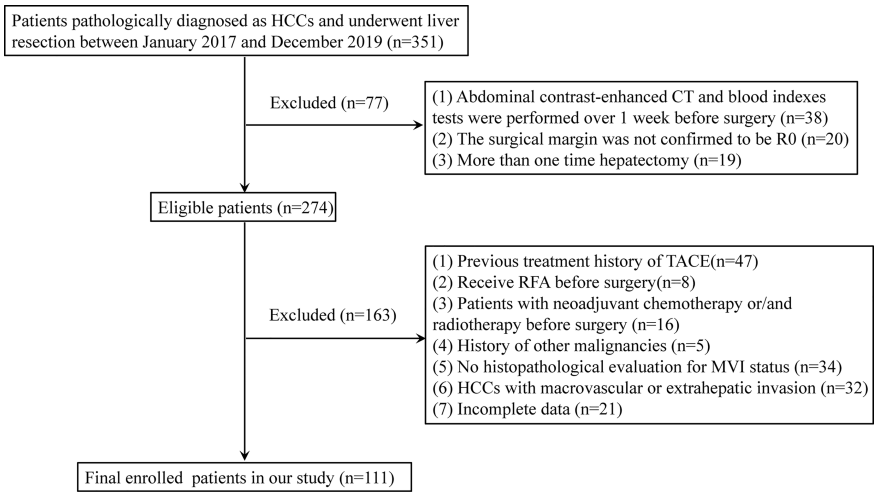

FIGURE 1 | Flowchart of the patients included in the analysis.

according to the three-tiered MVI grading system (17). Other pathological characteristics like satellite nodule and the Edmondson–Steiner classification were also collected.

Statistical Analysis

Continuous variables which were expressed as median (range) were compared using the Mann–Whitney *U* test. The χ^2 test or Fisher's exact test was used to calculate statistical differences of categorical variables. All variables related to the MVI and its M2 classification in the univariate analysis were regarded as candidates for multivariate logistic analysis. The least absolute shrinkage and selection operator (LASSO) regression model was used to reduce data dimensionality and select the most significant elements with non-zero coefficients (24). The integrated discrimination improvement (IDI) is the difference in the discrimination slopes for a prediction model with and without one variable, which indicates whether the discrimination slope of a model will improve if one important parameter is added. The net reclassification improvement (NRI) is an index that attempts to quantify how well a new model correctly reclassifies subjects. So IDI and NRI can be used for the comparison between an original model and a new model (the original model plus one additional component) (25).

The final predictors correlated with MVI and its M2 classification were determined by LASSO regression, logistic regression, and IDI and NRI analyses and used to establish the corresponding nomograms. The nomogram can proportionally convert each regression coefficient in the logistic regression to a scale of 0 to 100 points (26). The points of each independent variable were summed, and the predicted probabilities were derived from the total points. The predictive performance and accuracy of the nomograms were evaluated by AUC and calibration curve, respectively. Decision curve analysis (DCA) was performed by calculating the net benefits at different points of threshold probabilities to evaluate the clinical utility of the nomograms. In all analyses, P <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, IL, USA) and R version 4.0.3.

RESULTS

Clinicopathological Characteristics

A total of 111 patients with HCC were retrospectively enrolled in this study. The median age was 57 years (range 37–80), 97 (87.4%) patients were male, 14 (12.6%) patients were female, 40 (36.0%) patients had symptoms at diagnosis, and the median tumor size (longest tumor diameter) was 7 cm (range 1.5–22). Based on the eighth TNM staging system recommended by the AJCC, among 111 HCC patients, 8 cases (7.2%) were classified as stage I, 38 cases (34.2%) were classified as stage II, 60 cases (54.1%) were classified as stage III, and 5 cases (4.5%) were classified as stage IV. MVI was found in 72 of 111 (64.86%) patients, whereas M2 grade was presented in 47 of 72 (65.28%) MVI-positive patients. The detailed clinicopathological characteristics are listed in **Tables 1** and **2**.

Independent Significant Factors for the Presence of MVI and Its M2 Grade

In comparison of the clinicopathological characteristics between the MVI-positive and MVI-negative groups, eight variables, namely, clinical TNM stage, α-fetoprotein (AFP), Edmondson–Steiner classification, tumor size, tumor number, tumor capsule, tumor margin, and satellite nodule, were significantly associated with the MVI according to the univariate analysis (**Table 1**). Nevertheless, among MVI-positive cases, only clinical TNM stage, tumor number, tumor capsule, and tumor margin showed statistical correlation with M2 grade (**Table 2**). Furthermore, clinical TNM stage, Edmondson–Steiner classification, tumor size, tumor capsule, tumor margin, and AFP were found to be independent risk factors of MVI by

TABLE 1 | Clinical characteristics of HCC patients and their correlations with MVI status.

Variables	Total (*n* = 111)	MVI negative (*n* = 39)	MVI positive (*n* = 72)	*P*
Age (years), median (range)	57 (37–80)	56 (37–70)	58 (37–80)	0.814
Sex, *n* (%)				0.961
Male	97 (87.4)	34 (87.2)	63 (87.5)	
Female	14 (12.6)	5 (12.8)	9 (12.5)	
Symptoms at diagnosis				0.417
No	71 (64.0)	27 (69.2)	44 (61.1)	
Yes	40 (36.0)	12 (30.8)	28 (38.9)	
Edmondson–Steiner classification, n (%)				**<0.001**
I–II	62 (55.9)	31 (79.5)	31 (43.1)	
III–IV	49 (44.1)	8 (20.5)	41 (56.9)	
Clinical TNM stage, *n* (%)				**<0.001**
I	8 (7.2)	8 (20.5)	0 (0)	
II	38 (34.2)	24 (61.5)	14 (19.4)	
III	60 (54.1)	6 (15.4)	54 (75.0)	
IV	5 (4.5)	1 (2.6)	4 (5.6)	
Cirrhosis, *n* (%)				0.254
No	28 (25.2)	7 (17.9)	21 (29.2)	
Yes	83 (74.8)	32 (82.1)	51 (70.8)	
Tumor number, *n* (%)				**<0.001**
Solitary	61 (55.0)	31 (79.5)	30 (41.7)	
Multiple	50 (45.0)	8 (20.5)	42 (58.3)	
Tumor size (cm), median (range)	7 (1.5–22)	4 (2–14)	10 (1.5–22)	**<0.001**
Tumor capsule, n (%)				**<0.001**
Absent	55 (49.5)	5 (12.8)	50 (69.5)	
Incomplete	23 (20.7)	7 (17.9)	16 (22.2)	
Complete	33 (29.7)	27 (69.2)	6 (8.3)	
Tumor location, *n* (%)				0.699
Right lobe of liver	77 (69.4)	26 (66.7)	51 (70.8)	
Left lobe of liver	26 (23.4)	9 (23.1)	17 (23.6)	
Both lobe of liver	5 (4.5)	2 (5.1)	3 (4.2)	
Caudate lobe	3 (2.7)	2 (5.1)	1 (1.4)	
Tumor margin, *n* (%)				**<0.001**
Not smooth	52 (46.8)	6 (15.4)	46 (63.9)	
Smooth	59 (53.2)	33 (84.6)	26 (36.1)	
Satellite nodule, *n* (%)				**0.003**
Absent	61 (55.0)	29 (74.4)	32 (44.4)	
Present	50 (45.0)	10 (25.6)	40 (55.6)	
HBsAg, n (%)				0.834
Negative	36 (32.4)	12 (30.8)	24 (33.3)	
Positive	75 (67.6)	27 (69.2)	48 (66.7)	
AFP (ng/ml)				**<0.001**
<20	29 (26.1)	19 (48.7)	10 (13.9)	
20–400	30 (27.0)	11 (28.2)	19 (26.4)	
>400	52 (46.8)	9 (23.1)	43 (59.7)	
CEA (ng/ml), median (range)	2.62 (0.2–29.69)	2.9 (0.24–27.56)	2.21 (0.2–29.69)	0.369
ALT (U/L), median (range)	40 (3–209)	41 (8–209)	36.5 (3–108)	0.509
AST (U/L), median (range)	36 (3–383)	33 (4–383)	36.5 (3–149)	0.965
ALB (g/L), median (range)	39 (21–52)	38 (29–51)	39.5 (21–52)	0.260
PT (s), median (range)	11.9 (9.7–22.6)	12 (10.07–22.6)	11.825 (9.7–18.2)	0.413

MVI, microvascular invasion; TNM, tumor-node-metastasis, according to the eighth edition of the AJCC (American Joint Committee on Cancer) cancer staging manual; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; PT, prothrombin time. P: categorical variables—χ^2 test or Fisher's exact test; continuous variables—Mann–Whitney U test.
The bold value means statistical significance.

multivariate analysis; interestingly, when MVI was present, three variables of tumor number, tumor capsule, and tumor margin were highly associated with M2 grade from the result of multivariate analysis (**Table 3**).

Identification of Predictive Factors by LASSO Regression

In total, 19 variables were analyzed by LASSO regression and 8 candidate factors were determined to be associated with MVI (**Figure 2A**). These factors were clinical TNM stage, alanine aminotransferase (ALT), AFP, Edmondson–Steiner classification, tumor size, tumor capsule, tumor margin, and tumor number. Among the patients with MVI presence, clinical TNM stage, tumor capsule, tumor margin, and aspartate transaminase (AST) were selected and identified as risk factors of M2 grade by using LASSO regression analysis (**Figure 2B**). The coefficients of selected parameters associated with MVI and its M2 grade are shown in **Table S1**.

TABLE 2 | Clinical characteristics comparison in HCC patients with different degrees of MVI.

Variables	M1 (*n* = 25)	M2 (*n* = 47)	*P*
Age (years), median (range)	60 (37–80)	56 (39–79)	0.705
Sex, *n* (%)			0.710
Male	21 (84.0)	42 (89.4)	
Female	4 (16.0)	5 (10.6)	
Symptoms at diagnosis			0.452
No	17 (68.0)	27 (57.4)	
Yes	8 (32.0)	20 (42.6)	
Edmondson–Steiner classification, n (%)			0.620
I–II	12 (48.0)	19 (40.4)	
III–IV	13 (52.0)	28 (59.6)	
Clinical TNM stage, *n* (%)			**0.017**
I	0 (0)	0 (0)	
II	9 (36.0)	5 (10.6)	
III	16 (64.0)	38 (80.9)	
IV	0 (0)	4 (8.5)	
Cirrhosis, *n* (%)			0.280
No	5 (20.0)	16 (34.0)	
Yes	20 (80.0)	31 (66.0)	
Tumor number, *n* (%)			**0.026**
Solitary	15 (60.0)	15 (31.9)	
Multiple	10 (40.0)	32 (68.1)	
Tumor size (cm), median (range)	11 (2–20)	10 (1.5–22)	0.709
Tumor capsule, n (%)			**<0.001**
Absent	10 (40.0)	40 (85.1)	
Incomplete	10 (40.0)	6 (12.8)	
Complete	5 (20.0)	1 (2.1)	
Tumor location, *n* (%)			0.909
Right lobe of liver	18 (72.0)	33 (70.2)	
Left lobe of liver	6 (24.0)	11 (23.4)	
Both lobe of liver	1 (4.0)	2 (4.3)	
Caudate lobe	0 (0)	1 (2.1)	
Tumor margin, *n* (%)			**0.001**
Not smooth	9 (36.0)	37 (78.7)	
Smooth	16 (64.0)	10 (21.3)	
Satellite nodule, *n* (%)			0.213
Absent	14 (56.0)	18 (38.3)	
Present	11 (44.0)	29 (61.7)	
HBsAg, n (%)			0.861
Negative	8 (32.0)	16 (34.0)	
Positive	17 (68.0)	31 (66.0)	
AFP (ng/ml)			0.194
<20	6 (24.0)	4 (8.5)	
20–400	6 (24.0)	13 (27.7)	
>400	13 (52.0)	30 (63.8)	
CEA (ng/ml), median (range)	2.48 (1.04–29.69)	2.13 (0.2–28.69)	0.538
ALT (U/L), median (range)	44 (11–99)	35 (3–108)	0.456
AST (U/L), median (range)	37 (19–114)	36 (3–149)	0.239
ALB (g/L), median (range)	39 (32–51)	40 (21–52)	0.526
PT (s), median (range)	11.85 (10.6–18.2)	11.7 (9.7–15.2)	0.424

M1 and M2 classification based on the three-tiered microvascular invasion grading system. TNM, tumor-node-metastasis, according to the eighth edition of the AJCC (American Joint Committee on Cancer) cancer staging manual; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; PT, prothrombin time. P: categorical variables—χ^2 test or Fisher's exact test; continuous variables—Mann–Whitney U test.
The bold value means statistical significance.

Confirmation of the Best Prediction Model for MVI and M2 Grade

The base model (model 1) was then created by incorporating six variables (Edmondson–Steiner classification, clinical TNM stage, tumor size, tumor capsule, tumor margin, and AFP) determined to be associated with MVI both in logistic and LASSO analyses. By severally adding ALT and tumor number to model 1, we constructed two new models named model 2 and model 3. Taking model 1 as the reference, model 2 did not exhibit superiority for predicting MVI. Adding tumor number to model 1 did not appreciably change the AUC and IDI, but led to a significant improvement in the continuous NRI (cNRI) (**Table 4**), which indicated that model 2 was superior to model 1 in MVI prediction. Moreover, among HCC patients with MVI presence, tumor capsule and tumor margin were both confirmed by LASSO and logistic regression to be related with M2 grade.

TABLE 3 | Risk factors for MVI and its M2 grade identified by logistic multivariate analysis.

Factors	MVI presence			M2 degree of MVI presence		
	OR	95% CI	*P*	OR	95% CI	*P*
Edmondson–Steiner classification						
I–II	1			1		
III–IV	7.333	1.797–29.922	**0.005**	1.849	0.578–5.909	0.300
Clinical TNM stage						
I–II	1			1		
III–IV	6.031	1.577–23.061	**0.009**	3.906	0.986–15.473	0.052
Tumor number						
Solitary	1			1		
Multiple	3.885	0.817–18.460	0.088	3.200	1.168–8.770	**0.024**
Tumor size (cm)						
<5	1			1		
≥5	5.129	1.081–24.349	**0.040**	2.117	0.413–10.844	0.368
Tumor capsule						
Present	1			1		
Absent	6.174	1.775–21.475	**0.004**	7.772	2.411–25.052	**0.001**
Tumor margin						
Smooth	1			1		
Not smooth	4.999	1.620–15.430	**0.005**	6.578	2.246–19.266	**0.001**
Satellite nodule						
Absent	1			1		
Present	1.155	0.232–5.756	0.860	2.601	0.853–7.932	0.093
AFP (ng/ml)						
<20	1			1		
20–400	4.046	1.129–14.497	**0.032**	4.373	0.771–24.806	0.096
>400	9.322	2.586–33.613	**0.001**	4.089	0.823–20.319	0.085

MVI, microvascular invasion; M2 classification based on the three-tiered MVI grading system. TNM, tumor-node-metastasis, according to the eighth edition of the AJCC (American Joint Committee on Cancer) cancer staging manual; AFP, alpha fetoprotein.
The bold value means statistical significance.

So the second base model (model A) was established by incorporating tumor capsule and tumor margin. Subsequently, we developed model B, model C, and model D by respectively adding clinical TNM stage, AST, and tumor number to the base model A and found that model B and model D are better than model A for predicting M2 grade in the presence of MVI (model B vs. model A, cNRI = 0.507, $p = 0.017$; model D vs. model A, cNRI = 0.562, $p = 0.019$), whereas model C did not show any superiority in M2 prediction (**Table 4**), suggesting that clinical TNM stage and tumor number can be definitely considered as the risk factors of M2 grade when MVI is present.

Development and Validation of Nomograms for Predicting MVI and Its M2 Grade

A nomogram incorporating Edmondson–Steiner classification, clinical TNM stage, tumor size, tumor capsule, tumor margin, AFP, and tumor number was constructed for MVI prediction (**Figure 3A**). In the presence of MVI, a second nomogram for predicting M2 grade was developed by using four variables, namely, clinical TNM stage, tumor capsule, tumor margin, and tumor number (**Figure 3B**). Calibration curves of the two nomograms demonstrated good consistency between the predicted and observed results regarding the MVI status and its M2 classification (**Figure 3C**). The AUC of the nomogram predicting MVI was 0.926, and the AUC of the nomogram for M2 grade prediction in MVI-positive cases was 0.803 (**Figure 3D**).

Clinical Use of the Nomograms for MVI and Its M2 Grade Prediction

Each variable displayed in the two nomograms was assigned a risk score. The detailed scores of these variables are presented in **Table S2**. The final total scores that ranged from 0 to 407 (MVI nomogram) and 0 to 225 (M2 nomogram) were obtained by summing the scores of each variable. The optimal cutoff values of the total scores were confirmed by the maximum Youden index in ROC curve analysis (**Tables S3** and **S4**). Based on the cutoff scores of 172 from the MVI nomogram and 163 from the M2 nomogram, HCC patients were being divided into low- and high-risk groups. The high-risk groups had a significantly greater probability of having MVI and were classified as M2 grade (**Figure 4**). Then DCA results revealed that using the two nomograms to predict MVI and its M2 grade for almost all threshold probabilities at different points added more net benefit than the treat-all or treat-none strategies (**Figures 5A, B**), suggesting good clinical utility of the two nomograms. For the purpose of understanding their significance more intuitively, clinical impact curves of the nomograms for prediction in MVI and its M2 grade were plotted (**Figures 5C, D**), and the distance between the curve of the high-risk predicted number (the gray

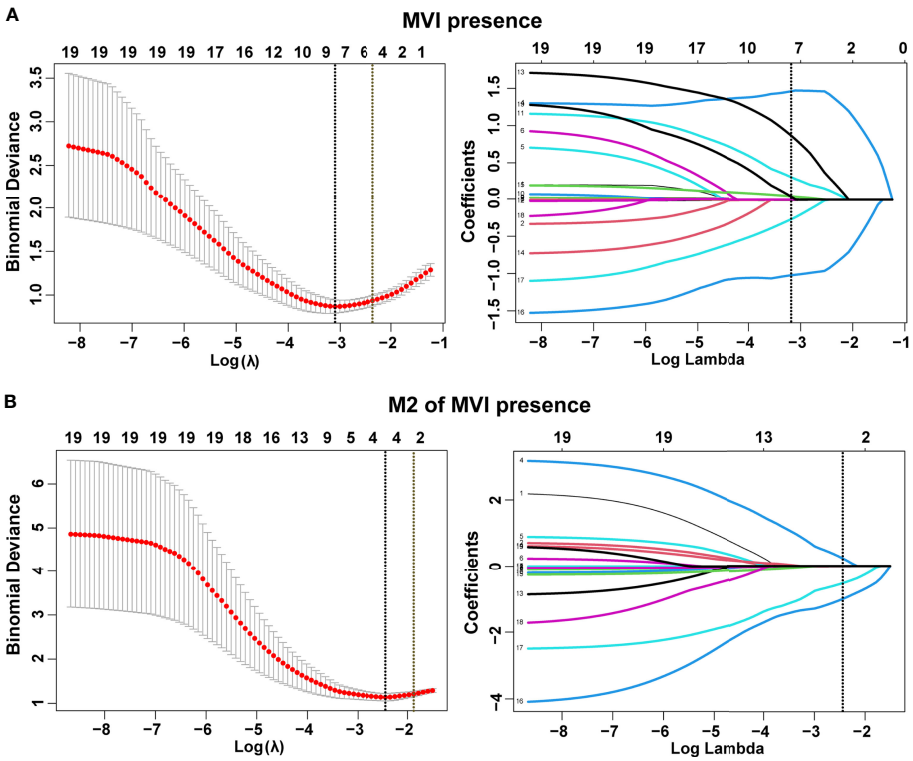

FIGURE 2 | Selection of demographic and clinical features using the least absolute shrinkage and selection operator (LASSO) regression model. Selection of tuning parameter (*λ*) in the LASSO model by three-fold cross-validation based on minimum criteria for MVI **(A)** and its M2 grade **(B)**. Dotted vertical lines were drawn at the optimal values using the minimum criteria and the 1 standard error of the minimum criteria (1-SE criteria). All features with non-zero coefficients are indicated on the right of **(A, B)**.

curve) and the curve of the high-risk actual number (the red curve) was very close in almost all high-risk threshold points, indicating that the two models had remarkable predictive power.

DISCUSSION

The long-term prognosis of HCC patients at early- to intermediate-stage after curative therapies is still poor, mainly due to the high recurrence rate after primary resection (7). Being considered as an important marker of HCC aggressive behavior, MVI could greatly affect intrahepatic metastasis of tumor cells *via* the portal circulation (27) and lead to tumor recurrence after curative surgery (28). Among MVI-positive cases, the M2 grade is an obvious indicator of HCC poor prognosis. The tumor microenvironment of HCC with MVI-M2 grade provides a favorable condition for tumor rapid growth and aggressive invasion, resulting in a true R0 surgical resection which is difficult to achieve (18). MVI and its M2 classification based on MVI-TTG only can be diagnosed by histopathological examination after surgical resection (17). Hence, it is important to find the significant risk factors of MVI and its M2 grade and develop prediction models by using these factors, which could provide optimal management decision. In the present study, approximately 64.86% of patients (72/111) with HCC harbored MVI, and among these MVI-positive cases, 47 patients (65.28%) were classified as M2 grade. Our analysis also suggested that later clinical tumor stage, higher AFP, more advanced Edmondson–Steiner classification, larger tumor size, tumor capsule absence, non-smooth tumor margin, and multiple tumor number were significantly associated with MVI, and patients with MVI-M2 among these MVI-positive cases were more likely to have later clinical tumor stage, absent tumor capsule, non-smooth tumor margin, and multiple tumor number.

Almost all studies indicated that tumor size was associated with MVI. However, the correlation between tumor size classification and MVI remained controversial. A study from an international multicenter database showed that the incidence of MVI increased with the tumor size of resected HCC (tumor size, MVI incidence: ≤3 cm, 25%; 3.1–5 cm, 40%; 5.1–6.5 cm, 55%; >6.5 cm, 63%) (29). Kim et al. (30) and Siegel et al. (31) respectively reported that tumor size more than 2 or 3 cm was a risk factor of MVI. In our study, we found that tumor size was also correlated with MVI; especially HCCs more than 5 cm increased the probability of MVI formation. Interestingly, in MVI-positive patients, there is no significant difference in tumor size between M1 and M2 grades. It is speculated that tumor size may only play a role in tumor cells if they can invade the microvessels. Once MVI is present, the

TABLE 4 | Comparison of different prediction models for estimating the risk of MVI and its M2 grade.

Model	AUC (95% CI)	*P*	IDI (95% CI)	*P*	cNRI (95% CI)	*P*
MVI positive						
Model 1 (base model)	0.921 (0.868–0.975)	Ref		Ref		Ref
Model 2	0.925 (0.877–0.975)	0.562	–0.001 (–0.013 to 0.012)	0.984	0.256 (–0.125 to 0.638)	0.187
Model 3	0.926 (0.877–0.974)	0.569	0.003 (–0.012 to 0.018)	0.683	0.756 (0.416 to 1.097)	**<0.001**
M2 grade of MVI						
Model A (base model)	0.764 (0.649–0.879)	Ref		Ref		
Model B	0.799 (0.691–0.908)	0.175	0.024 (–0.021 to 0.069)	0.291	0.507 (0.092 to 0.923)	**0.017**
Model C	0.778 (0.660–0.896)	0.533	0.004 (–0.002 to 0.009)	0.203	0.238 (–0.225 to 0.701)	0.313
Model D	0.773 (0.652–0.893)	0.684	0.008 (–0.012 to 0.027)	0.454	0.562 (0.094 to 1.029)	**0.019**

Model 1 = Edmondson–Steiner classification + clinical TNM stage + tumor size + tumor capsule + tumor margin + AFP; model 2 = model 1 + ALT; model 3 = model 1 + tumor number; model A = tumor capsule + tumor margin; model B = model A+ clinical TNM stage; model C = model A + AST; model D = model A + tumor number.
AUC, area under curve; IDI, integrated discrimination improvement; cNRI, continuous net reclassification improvement.
The bold value means statistical significance.

tumor size perhaps has little to do with the site number of MVI. According to histological examination, MVI-positive tumors have a strong aggressive tendency to invade the tumor encapsulation, making the tumor margin irregular (32). Among MVI-positive patients, 67% HCCs were found irregular or had non-smooth margin (33). Consistently, in this study, absent tumor capsule and non-smooth tumor margin were demonstrated to be the independent risk factors of MVI. Besides, we also found that tumor capsule and tumor margin have a significant difference between M1 and M2 grades in MVI-positive cases.

What is more, several studies have identified that multiple tumors and elevated AFP levels are associated with an increased probability of vascular invasion in HCCs (9, 34, 35). Similarly, our study demonstrated that AFP was also significantly associated with MVI presence, but the tumor number did not seem to be an independent risk factor of MVI. The *P*-value (0.088) of tumor number in multivariate analysis for MVI risk factor estimation was close to 0.05, which might show statistical significance if this study had a much larger sample size. In contrast, high serum AFP level did not appear to correlate with MVI-M2 grade, while MVI-positive patients with multiple tumors were more likely to be M2 grade according to our multivariate logistic analysis, meaning that the serum AFP level does not affect the number of MVI sites but cases with multiple tumors have more MVI sites. Clinical TNM stage is an important reference for evaluating the prognosis of HCC patients and is a comprehensive variable that integrates tumor size, number of tumor lesions, lymph node metastasis, and distant metastasis, and generally assessed by radiological imaging before surgery. The Edmondson–Steiner classification represents the degree of HCC differentiation. The preoperative true diagnosis

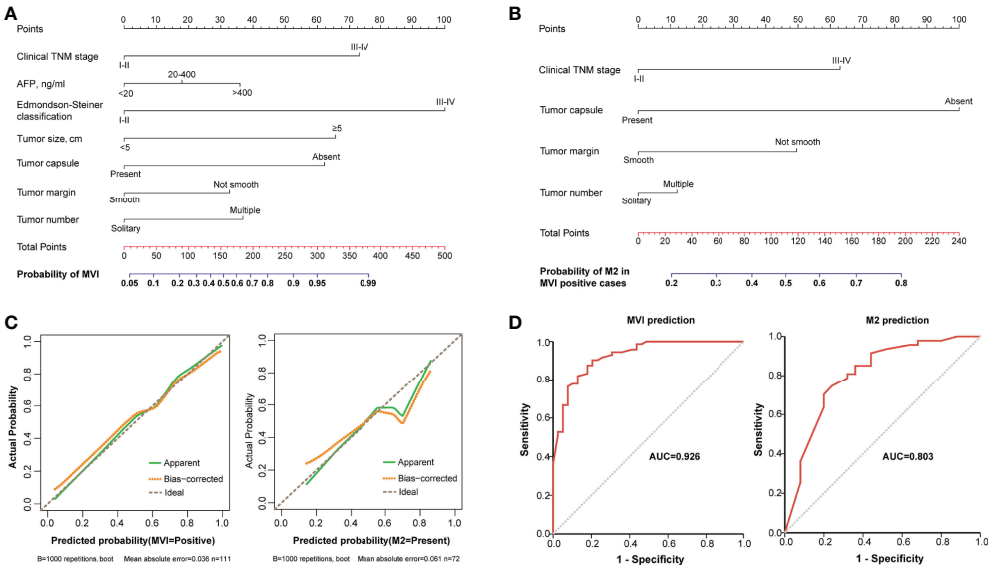

FIGURE 3 | The nomograms and their calibration and discrimination. **(A)** The MVI nomogram was built by incorporating clinical TNM stage, AFP, Edmondson–Steiner classification, tumor size, tumor capsule, tumor margin, and tumor number. **(B)** Among the MVI-positive cases, clinical TNM stage, tumor capsule, tumor margin, and tumor number were used to establish another nomogram for predicting M2 grade. Locate the patient's characteristic on a variable row and draw a vertical line straight up to the points' row (top) to assign a point value for the variable. Adding up the total number of points and drop a vertical line from the total points' row to obtain the probability of predictive outcomes. **(C)** The calibration curves of the two nomograms based on internal validation with a bootstrap resampling frequency of 1,000. **(D)** The ROC curves with AUCs of 0.926 and 0.803 to demonstrate the discriminatory ability of the two nomograms.

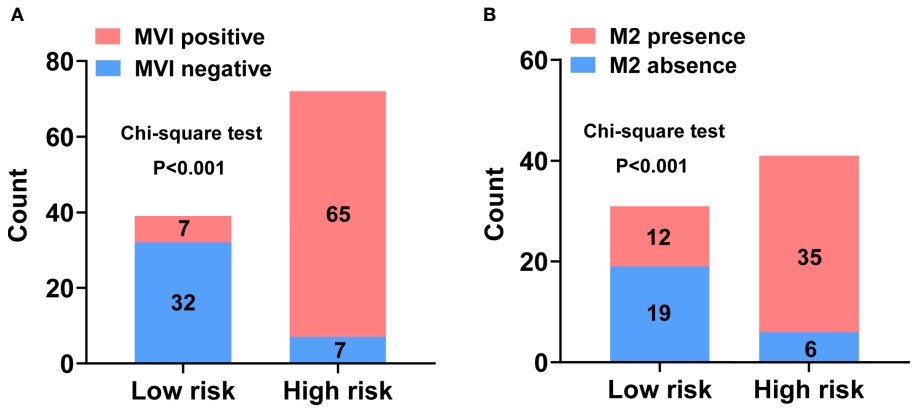

FIGURE 4 | Discriminatory power of the nomograms for MVI and its M2 grade with bar charts. Risk classification of the predictive nomograms conducted by the maximum Youden index, and the performance in distinguishing the MVI **(A)** and its M2 grade **(B)**. *P*-values were calculated by the chi-square test.

of HCC is usually by liver biopsy. When HCC diagnosis was confirmed, information of the HCC differentiation also can be obtained simultaneously. In multivariate logistic analysis, we found that clinical TNM stage and Edmondson–Steiner classification were significantly related to MVI yet not the independent predictors of MVI-M2 grade. From the result of multivariate logistic analysis for M2 risk factors, clinical TNM stage *P*-value (0.052) was extremely close to 0.05. Meanwhile, given the remarkable impact of clinical TNM stage on the prognosis of HCC patients, we speculated that this variable may also be a predictor of MVI-M2 grade.

Subsequently, we found that clinical TNM stage, AFP, Edmondson–Steiner classification, tumor size, tumor capsule, tumor margin, tumor number, and ALT were risk factors for

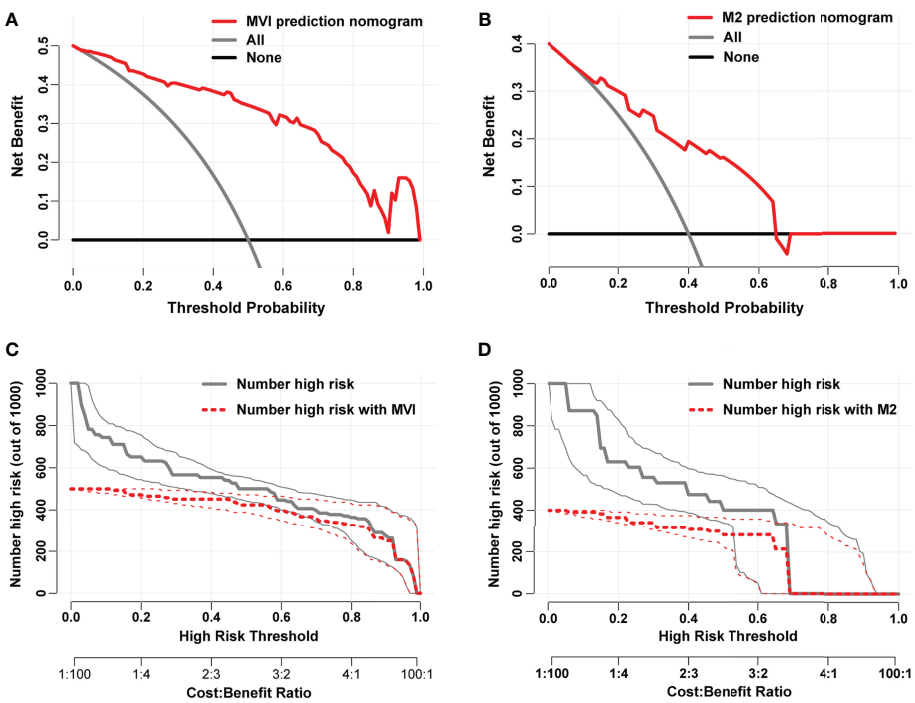

FIGURE 5 | Decision curves of the nomograms for predicting presence of MVI **(A)** and its M2 grade **(B)**. The horizontal solid black line represents the hypothesis that no patients experienced the presence of MVI or its M2 grade, and the solid gray line represents the hypothesis that all patients met the endpoint. Clinical impact curves of the nomograms for MVI and its M2 grade prediction, respectively, were plotted in **(C, D)**. At different threshold probabilities within a given population, the number of high-risk patients and the number of high-risk patients with the outcome were shown.

MVI formation based on the LASSO regression analysis. Also, in patients with MVI presence, clinical TNM stage, AST, tumor capsule, and tumor margin were related to M2 classification. However, in the logistic regression results, ALT and tumor number were not independent risk factors for MVI, and clinical stage and AST were not associated with M2 grade when MVI was present. In addition, according to the LASSO regression results, there was no correlation between tumor number and M2 grade among MVI-positive patients. Therefore, in order to further explore whether ALT and tumor number are independent risk factors for the formation of MVI, we established model 2 and model 3 by respectively adding ALT and tumor number to model 1 (base model incorporating clinical TNM stage, AFP, Edmondson–Steiner classification, tumor size, tumor capsule, and tumor margin). The cNRI analysis revealed a remarkable MVI prediction improvement in model 3, whereas no significant MVI prediction improvement was observed in model 2 compared with model 1, which means that tumor number can be considered as an independent predictive factor of MVI presence. Additionally, to further clarify whether clinical stage, tumor number, and AST correlate with M2 classification in the presence of MVI, we constructed three new models named model B, model C, and model D by adding clinical tumor stage, AST, and tumor number, respectively, to model A (base model including tumor capsule and tumor margin). Taking model A as reference, the cNRI analysis showed that model B and model D significantly improved the M2 prediction, but model C did not have improvement of predictive ability for M2 in MVI-positive cases, indicating that clinical tumor stage and tumor number are the true predictors of M2 grade.

The nomogram has been recognized as a user-friendly and practical prediction tool with high accuracy and good discriminative power and is widely used in the evaluation of prognosis or an outcome event (36, 37). Hence, a nomogram was developed for MVI prediction by incorporating Edmondson–Steiner classification, clinical TNM stage, tumor margin, AFP level, tumor size, tumor capsule, and tumor number, and a nomogram including clinical TNM stage, tumor capsule, tumor margin, and tumor number was also built for predicting M2 classification in the presence of MVI. Both nomograms demonstrated good consistency between the predicted probabilities and the actual observations according to the optimal calibration curves. Furthermore, satisfactory diagnostic performance was found in these two nomograms with AUCs of 0.926 (AUC_{MVI}) and 0.803 (AUC_{M2}). Then the cutoff values of total points were determined as 172 in the MVI nomogram and 163 in the M2 nomogram according to the maximum Youden index from ROC analysis. Patients with a total score of >172 were a high-risk subgroup of MVI and those with a score of >163 were considered as high-risk of M2 grade when MVI was present, which could guide us to make the best treatment decision. Moreover, we also opted to conduct a DCA to determine the clinical utility of our nomogram. DCA is a novel method to evaluate the clinical benefits of diagnostic tests and prediction models (38). Here, great net benefit of the established nomograms with the risk threshold more than 0.2 was shown in DCA, indicating good clinical utility of the two nomograms. In addition, excellent predictive power of the two nomograms was further determined by plotting the clinical impact curves.

Although most previous studies generally split the dataset randomly into two groups of training set and validation set, this was not adopted in our study due to limitation of sample size. Besides, this approach did not fully utilize all available data to develop the prediction model, resulting in statistical inefficiency or even waste (39). HCC patients of our study both had positive and negative HBsAg, and the established nomogram showed satisfactory discriminative performance regardless of HBV infection, indicating that our prediction model might comparably be suitable for HCC caused by viral hepatitis and non-viral hepatitis. It is a pity that this study still had several limitations. Firstly, this was a retrospective study with a small sample size and had an inevitable case selection bias. So a large sample size prospective study with balanced populations is required to further confirm the reliability of our nomograms in the future. Secondly, our study was only conducted at a single institute and did not have any validation. It is necessary to validate our results by using data from multiple centers. Finally, the nomograms were established just based on the limited clinical data; thus, specific genetic markers need to be identified and incorporated into nomograms to further advance the prediction accuracy of the nomograms.

In conclusion, the Edmondson–Steiner classification, clinical TNM stage, tumor margin, AFP level, tumor size, tumor capsule, and tumor number were identified as significant predictive factors for MVI in HCC patients, and clinical TNM stage, tumor capsule, tumor margin, and tumor number were confirmed as independent predictors of M2 grade among MVI-positive cases. Then two wieldy nomograms were developed by incorporating these variables above, making individualized prediction of MVI and its M2 grade more objective and accurate. Judging from the two nomogram scoring systems, more aggressive treatment may be recommended to reduce potential future recurrence if patients are considered as high risk of MVI and perhaps classified into M2 grade. Last but not least, our nomograms can improve individualized therapy design and facilitate monitoring plan selection, which may lead to effective and curative treatment initiation for HCC patients.

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 Zhejiang Cancer Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SW and SC conceived the idea and designed the study. RR and JY collected the data. CW and YG analyzed the data. SC, CW, and YG drafted the manuscript. All authors contributed to the article and approved the submitted version.

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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.2021.774800/full#supplementary-material

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Nomograms Incorporating the CNLC Staging System Predict the Outcome of Hepatocellular Carcinoma After Curative Resection

Rui Liao[1*†], *Xu-Fu Wei*[1†], *Ping Che*[2,3†], *Kun-Li Yin*[1] *and Lei Liu*[1]

[1] *Department of Hepatobiliary Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China,* [2] *Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China,* [3] *Department of Pediatric Surgery, Maternity and Child Health Hospital of Chongqing Hechuan, Chongqing, China*

Purpose: Prediction models of postoperative outcomes of patients with hepatocellular carcinoma (HCC) after surgery based on the China liver cancer (CNLC) staging system are rare. This study aimed to compare the prognostic abilities of CNLC, Tumor-Node-Metastasis (TNM) 8th edition, and Barcelona Clinic Liver Cancer (BCLC) staging systems for HCC after curative resection. We developed two nomograms incorporating the CNLC staging system to predict the postoperative recurrence-free survival (RFS) and overall survival (OS) of HCC patients.

Patients and methods: The prognostic abilities of the CNLC, TNM and BCLC staging systems for HCC after curative resection were compared using receiver operating characteristic (ROC) curves. Two nomograms incorporating five selected risk factors were constructed based on multivariate Cox regression in the primary cohort of 312 HCC patients. It was validated with an independent validation cohort of 130 HCC patients. The predictive performance and discrimination ability of the two nomograms were further evaluated and compared with those of the TNM and BCLC staging systems.

Results: The CNLC staging system had a higher area under the receiver operating characteristic curve (AUROC) value for both OS (AUC=0.692) and RFS (AUC=0.673) than the TNM (ROC=0.667 for OS and 0.652 for RFS) and BCLC (ROC=0.671 for OS and 0.670 for RFS) staging systems. The independent predictors of OS (cirrhosis, gamma-glutamyl transpeptidase (GGT), tumor differentiation and CNLC staging system) and RFS (α-fetoprotein (AFP) and CNLC staging system) were incorporated into the two nomograms. The OS and RFS nomograms consistently outperformed the TNM and BCLC staging systems in the primary cohort. These results were verified in the validation cohort. In the 442 patients with HCC, the RFS nomogram could predict early recurrence very well.

Conclusion: The two proposed nomograms incorporating the CNLC staging system can predict the outcomes of patients with HCC after curative hepatectomy in clinical practice.

Keywords: hepatocellular carcinoma, China liver cancer staging system, nomogram, surgery, recurrence, prognosis

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Benedetto Ielpo,
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Chihao Zhang,
Shanghai Jiao-Tong University, China

***Correspondence:**
Rui Liao
liaorui99@163.com

[†]These authors have contributed equally to this work

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor mainly caused by hepatitis B (HBV) or C viral (HCV) infection and it accounts for the majority of primary liver cancers. Globally, the incidence of HCC is steeply rising, and currently, it ranks as the fourth most common cause of cancer-related death in 2018 with a notably poor prognosis (1). Unfortunately, most HCC patients are diagnosed at advanced disease stages and miss the opportunity for curative resection (e.g., hepatectomy and liver transplantation) (2). Even though curative therapies remain a treatment option available to some HCC patients, their long-term outcomes are still generally poor due to their high rate of tumor recurrence (3). Thus, it is of paramount importance to establish effective methods to stratify optimal candidates for curative surgery and individualize anticancer treatment response surveillance.

To date, a number of risk factors have been reported to predict the outcomes and prognosis of HCC. Among them, the severity of liver dysfunction, vascular invasion, tumor size and number, and the presence of metastases are considered to be the most important factors in determining survival (4). Currently, there are more than 15 clinical staging systems including these prognostic factors, such as the (1) American Joint Commission on Cancer (AJCC) seventh edition (5), (2) the Barcelona Clinic Liver Cancer (BCLC) system (6), (3) Cancer of the Liver Italian Program (CLIP) system (7), (4) Japan Integrated Staging Score (JIS) system (8), (5) Okuda staging system (9), (6) Vauthey's system (10), (7) the albumin-bilirubin (ALBI) grading system (11), and (8) the Hong Kong Liver Cancer staging system (12). Although these staging systems could guide practitioners to the best options for therapeutic approaches, presently, a widely accepted optimal prognostic system is not available, particularly for surgical candidates.

Globally, approximately half of newly diagnosed HCC cases occur in China with an HBV infection background. In 2017, the China liver cancer (CNLC) staging system was established by Chinese experts according to recent HCC prognostic evidence, with subsequent modifications and updates for treatment allocations in 2019 (13–15). A recent comparative study (16) found that the BCLC system and the CNLC classification, as evidence-based staging systems and treatment algorithms, were useful in assisting treatment selection. Moreover, the CNLC staging system seems to perform better for HCC patients than the BCLC system. However, they often have a lower predictive ability than that of genuine prognostic scores due to structural variables not prognostically considered in real-life populations. Therefore, they result in a suboptimal prognostic performance (C index<0.7), suggesting that some key factors need to be incorporated into these systems to achieve substantial improvements for the prognostic estimation of HCC patient outcomes (16).

Compared to traditional staging systems, we have developed several nomograms for predicting the survival and recurrence of HCC that showed higher prognostic power than traditional staging systems (e.g., BCLC, TNM, etc.) (17–20). In this study, we compared the prognostic performance of some key risk variables and set up two reliable nomograms incorporating the CNLC staging system, and they could provide more accurate estimations of the prognosis of patients with HCC.

MATERIALS AND METHODS

Patients and Study Design

The patients enrolled in the study were from the First Affiliated Hospital of Chongqing Medical University between January 2014 and December 2015. In this retrospective study, a total of 531 consecutive patients were pathologically diagnosed with primary HCC and underwent curative resection. Eighty-nine patients were excluded according to the inclusion and exclusion criteria: (1) all patients had valid and reliable laboratory test data; (2) no preoperative extrahepatic metastases; (3) no anticancer treatments before the operation; (4) mayor R0 curative resection of all tumor nodules; and (5) complete patient records and follow-up data. Finally, 442 patients qualified for this study as a primary cohort (January 2014 to June 2015, n=312) to develop the nomograms and a validation cohort (July 2015 to December 2015, n=130). This study was performed in compliance with the 1975 Helsinki Declaration and was approved by the Ethics Review Committee of the First Affiliated Hospital of Chongqing Medical University. Informed consent to participate in this study was obtained from the research subjects prior to study commencement. The study participants also gave consent to have their data published.

Follow-Up

After discharge from the hospitals, all patients underwent follow-up every 3 months in the first 2 years and every 6 months afterward until signs of recurrence emerged over the next 3 to 5 years. During each regular surveillance for recurrence, serum α-fetoprotein (AFP), serum biochemistry, abdomen ultrasonography and chest and abdominal computed tomography (CT) examinations were conducted. Patients with recurrence received further treatment, including a second liver resection, radiofrequency ablation, transcatheter arterial chemoembolization or symptomatic treatment, according to the tumor size, site, number, hepatic functional reserve, extent of disease and general health of the patient. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and recurrence. Overall survival (OS) was defined as the interval between the date of surgery and death or the last follow-up. Recurrence was subdivided into early (≤ 24 months) and late recurrence (> 24 months) (17).

Prognostic Nomograms

The two nomograms were built based on the results of the multivariable analyses of RFS and OS in the primary cohort. Tumor number, tumor size and vascular invasion were not included in the nomograms because they are structural variables of the CNLC staging system, which was incorporated into the two nomograms. The final model was determined by a backward step-down selection process. Discrimination was evaluated by calculating the C-index. The values of the C-index were used to assess the discrimination ability (0.5–1.0).

Calibration plots were used to compare the predicted survival by the Kaplan–Meier curves of the quartiles of predictions. Bootstraps with 1000 resamples were used for both the validation of the nomograms and for calibration assessment (17–20).

Statistical Analysis

Statistical analyses were performed using SPSS 24.0 (SPSS, Inc., Chicago, IL, USA) and the rms package in R version 3.4.0 (http://www.r-project.org/). The χ^2 test or Fisher's exact test was used to compare the categorical variables. Continuous variables were compared using Student's t-tests with a normal distribution or nonparametric Mann–Whitney U-tests with an irregular distribution and reported as the mean ± standard deviation (SD). The sensitivity and specificity were defined by receiver operating characteristic (ROC) curves. Pearson's or Spearman's ρ coefficient tests were used to analyze the correlation between variables. RFS and OS curves were calculated by Kaplan–Meier survival estimates and compared using the log-rank test. Factors found to be significant were subsequently enrolled in the multivariable Cox proportional hazard regression models.

RESULTS

Baseline Characteristics

The clinical baseline characteristics of the 442 HCC patients in the primary and validation cohorts are described in **Table 1**. Both cohorts were mostly comprised of men (84.6% and 85.4%) and were similar in age composition. Moreover, the majority of the patients were HBsAg positive (85.6% and 88.5%) and had cirrhosis (86.9% and 93.1%). Vascular invasion occurred in 44.2% and 55.8% of patients, and the median tumor sizes were 5.5 and 4.0 cm in the primary cohort and the validation cohort, respectively.

OS and RFS in the Two Cohorts

The median follow-up was 54.0 months for the entire cohort, 55.5 months for the primary cohort, and 50.5 months for the validation cohort. In the primary cohort, the median OS and RFS were 36.5 (range, 1.0–81.5 months) and 34.0 months (range, 1.0–78.5 months), respectively. The 1-, 3-, and 5-year OS rates were 82.2%, 68.4% and 43.5%, respectively. The 1-, 3-, and 5-year RFS rates were 70.6%, 51.4% and 33.3%, respectively. In the validation cohort, the median OS and RFS were 37.1 (range, 1.0–65.0 months) and 32.5 months (range, 1.0–64.5 months), respectively. The 1-, 3-, and 5-year OS rates were 80.8%, 65.4% and 42.3%, respectively. The 1-, 3-, and 5-year RFS rates were 67.1%, 47.4% and 31.8%, respectively.

Prognostic Abilities of the CNLC, BCLC and TNM Staging Systems

In the primary cohort, the CNLC, BCLC and TNM staging systems all predicted the OS (P<0.01) and RFS (P<0.01) of patients with HCC after curative resection (**Figures 1A–C, E–G**). Receiver operating characteristic (ROC) curve analyses showed that the CNLC staging system (ROC=0.692 for OS and 0.673 for RFS) performed better for HCC patients than the BCLC (ROC=0.671 for OS and 0.670 for RFS) and TNM (ROC=0.667 for OS and 0.652 for RFS) staging systems (**Figures 1D, H**). The validation cohort had similar data (**Figure 2**), which is consistent with Vitale's recent report (16).

Independent Prognostic Factors in the Primary Cohort

In univariate analyses (**Table 2**), gamma-glutamyl transpeptidase (GGT, P<0.001 and =0.020), alpha-fetoprotein (AFP, both P<0.001), tumor number (P=0.002 and <0.001), vascular invasion (both P<0.001), tumor differentiation (P<0.001 and =0.020), tumor size (both P=0.001) and CNLC staging system (both P<0.001) were identified as significant prognostic factors for OS and RFS in the primary cohort, respectively. Both

TABLE 1 | Baseline of Patient Characteristics.

Characteristics	Primary cohort n = 312	Validation cohort n = 130	P-value
Age, yr, median, (range)	51.5 (18-80)	51.5 (25-78)	0.512
Gender (Female/Male)	48/264 (15.4%/84.6%)	19/111 (14.6%/85.4%)	0.533
Cirrhosis (yes/no)	271/41(86.9%/13.1%)	121/9 (93.1%/6.9%)	0.060
GGT, U/L, median (range)	64.0 (8.0-811.0)	61.0 (13.0-513.0)	0.252
ALB, g/L, median (range)	42.0 (28.0-53.0)	43.0 (31.0-54.0)	0.335
TBIL, μmol/L, median (range)	15.4 (4.4-75.2)	10.75 (4.5-34.4)	<0.001
AFP, ng/ml, median (range)	132.0 (0-60500.0)	130.0 (0-60500.0)	0.223
HBsAg (Positive/Negative)	267/45 (85.6%/14.4%)	115/15 (88.5%/11.5%)	0.420
Tumor number (single/multiple)	229/83 (73.4%/26.6%)	117/13 (90.0%/10.0%)	<0.001
Vascular invasion (yes/no)	138/174 (44.2%%/55.8%)	37/93 (28.5%/71.5%)	0.002
Tumor differentiation (I-II/III-IV)	174/138 (55.8%/44.2%)	95/35 (73.1%/26.9%)	0.001
Tumor size, cm, median (range)	5.5 (0.9-23.0)	4.0 (1.5-21.0)	0.002
BCLC stage (0-A/B/C)	136/35/141 (43.6%/11.2%/45.2%)	57/34/39 (43.8%/26.2%/30%)	0.009
TNM stage (I/II/III)	139/101/72 (44.6%/32.4%/23.0%)	85/42/3 (65.4%/32.3%/2.3%)	<0.001
CNLC stage (Ia/Ib/IIa/IIb/IIIa)	54/93/26/4/135 (17.3%/29.8%/8.3%/1.3%/43.3%)	56/27/8/3/36 (43.0%/20.8%/6.2%/2.3%/27.7%)	<0.001

GGT, gamma-glutamyl transpeptidase; ALB, Albumin; TBIL, total bilirubin; AFP, alpha fetoprotein; HBsAg, hepatitis B virus surface antigen; BCLC, Barcelona Clinic Liver Cancer; TNM, Tumor-Node-Metastasis; CNLC, China liver cancer staging system.

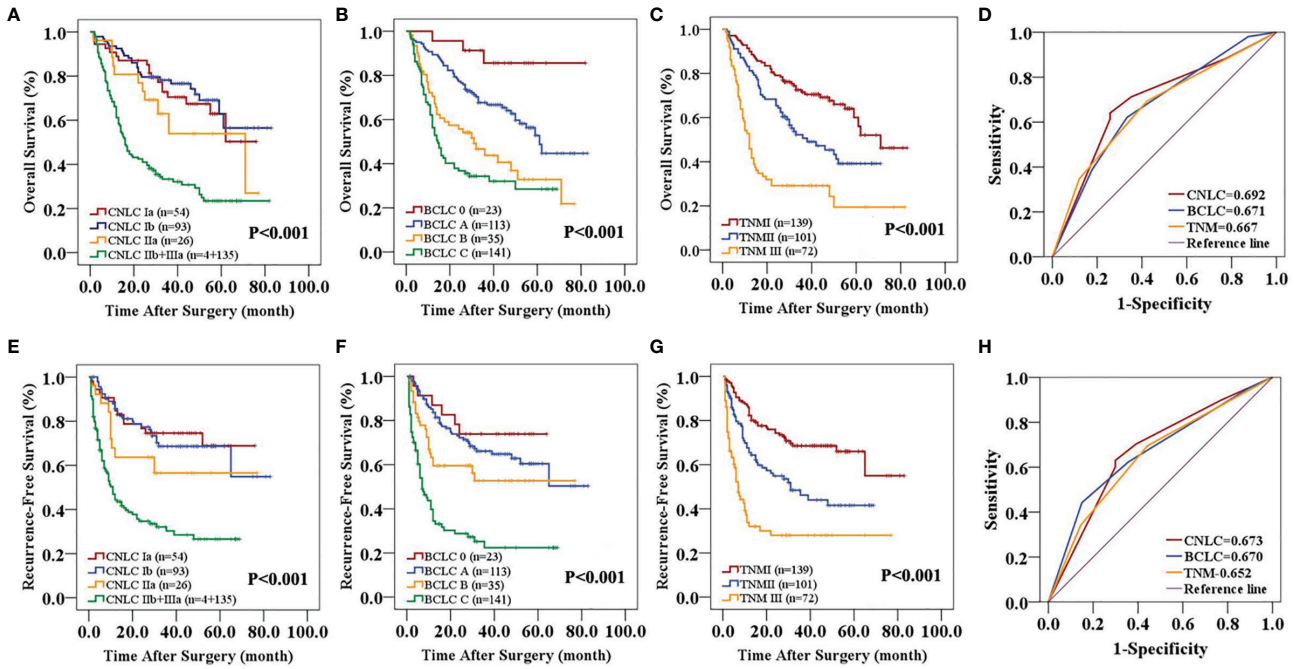

FIGURE 1 | Predictive accuracy comparison of the three staging systems for the prognosis of patients with HCC in the primary cohort. CNLC **(A, E)**, BCLC **(B, F)** and TNM 8th edition **(C, G)** staging systems are associated with OS **(A–C)** and RFS **(E–G)** of HCC after curative resection. ROC curves were used to compare the predictive accuracy of the three staging systems for assessing OS **(D)** and RFS **(H)** rates in the primary cohort.

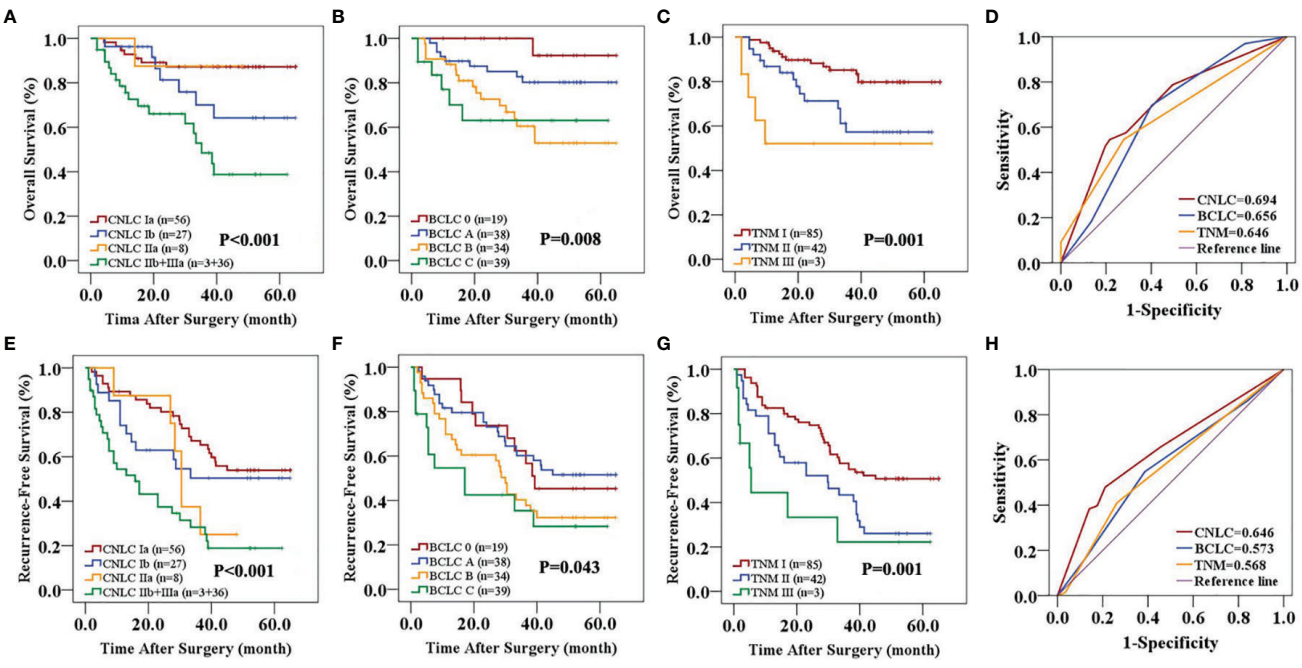

FIGURE 2 | Predictive accuracy comparison of the three staging systems for the prognosis of patients with HCC in the validation cohort. CNLC **(A, E)**, BCLC **(B, F)** and TNM 8th edition **(C, G)** staging systems are associated with OS **(A–C)** and RFS **(E–G)** of HCC after curative resection. ROC curves were used to compare the predictive accuracy of the three staging systems for assessing OS **(D)** and RFS **(H)** rates in the validation cohort.

TABLE 2 | Multivariate Analysis of OS and RFS of HCC in primary cohort.

Factors	OS		RFS	
	HR (95%CI)	P-value	HR(95%CI)	P-value
AFP (>20/≤20 ng/ml)	–	NS	1.615 (1.089-2.396)	0.017
Cirrhosis (yes/no)	2.137 (1.154-3.956)	0.016	–	NA
GGT (>64/≤64 U/L)	1.222 (1.078-1.384)	0.002	–	NS
ALB (>42/≤42 g/L)	–	NS	–	NA
Tumor differentiation (I-II/III-IV)	1.776 (1.287-2.449)	<0.001	–	NS
CNLC (Ia/Ib/IIa/IIb/IIIa)	1.450 (1.303-1.614)	<0.001	1.424 (1.273-1.592)	<0.001

Multivariate analysis, Cox proportional hazards regression model. HCC, hepatocellular carcinoma; OS, Overall survival; RFS, Recurrence-free survival; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; GGT, gamma-glutamyl transpeptidase; ALB, Albumin; CNLC, China liver cancer staging; NS, not significance, NA, not adopted.

cirrhosis (P=0.004) and albumin (ALB, P=0.02) could predict OS alone. Tumor number, tumor size and vascular invasion were not included in subsequent multivariable and nomograms because they are structural variables of the CNLC staging system. Multivariable (**Supplementary Table 1**) analyses demonstrated that cirrhosis (P=0.016), GGT (P=0.002), tumor differentiation (P<0.001) and the CNLC staging system (P<0.001) were independent prognostic factors of OS. Moreover, AFP (P=0.017) and the CNLC staging system (P<0.001) were related to RFS.

Predictive Performance of the Nomograms

The two prognostic nomograms comprised the CNLC staging system and several other independent OS and RFS prognostic factors were derived from the primary cohort (**Figure 3**). The C-indices of the OS and RFS nomograms were 0.743 (95% CI: 0.707–0.779) and 0.701 (95% CI: 0.659–0.739), respectively, which were higher than those of the CNLC staging system (C-index: 0.665 for OS and 0.676 for RFS) (**Supplementary Table 2**). Similarly, the OS and RFS nomograms showed the largest AUROCs (0.736 for OS and 0.715 for RFS) (**Figures 4A, B**) compared with the CNLC staging system. The results suggest that the two nomograms had more accurate OS and RFS prognostic power than the CNLC staging system in patients with HCC after curative hepatectomy. The OS and RFS probability calibration plots showed acceptable overall consistency between the two nomograms for predictions and actual observations in the primary cohort at 1, 3 and 5 years after surgery (**Figure 5**).

Validation of the Nomograms

Comparing the tumor characteristics, although some patient demographics in the validation cohort were different from those in the primary cohort, the nomograms still had powerful predictive abilities for the HCC patients in the validation cohort.

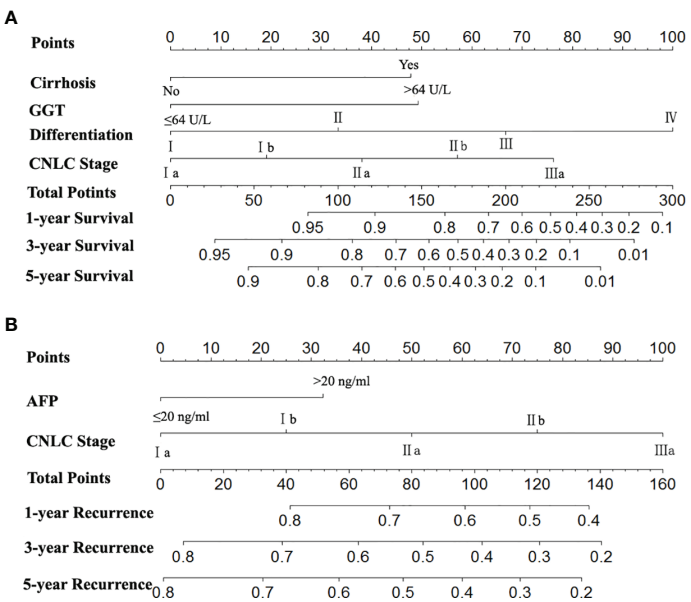

FIGURE 3 | Nomograms for predicting survival and recurrence of HCC patients after surgery. To calculate the probability of OS **(A)** and RFS **(B)**, straight upward lines are drawn to determine the points accrued. The sum of these points is plotted on the total points bar to the probability to yield the 1-, 3-, and 5-year survival or recurrence rates.

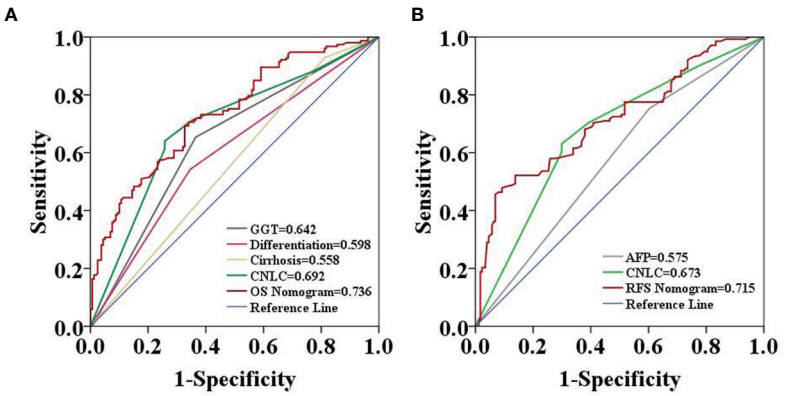

FIGURE 4 | Predictive accuracy comparison of each variable included in the OS **(A)** and RFS **(B)** nomograms by ROC curve analyses in the primary cohort. The ROC curves showed that the two nomograms were superior to the other variables in predictive accuracy.

The C-indices of the nomograms for predicting OS and RFS were 0.739 (95% CI: 0.656–0.822) and 0.672 (95% CI: 0.641–0.703), respectively. The C-indices of OS and RFS for the CNLC staging system were 0.687 (95% CI: 0.592–0.780) and 0.650 (95% CI: 0.591–0.709), respectively. The ROC analyses showed that the two nomograms had larger AUCs (0.750 for OS and 0.782 for RFS) than the CNLC staging system (0.694 for OS and 0.646 for RFS, **Figure 6**). Both the OS and RFS probability calibration plots had good agreement between predictions and observations in the probability of 1-, 3- and 5-year recurrence and survival (**Figure 7**).

The Predictive Performance of the RFS Nomogram for Early Recurrence

In the 442 patients with HCC, there were 168 patients (123 and 45 patients in the primary and validation cohorts, respectively) with early recurrence (ER, ≤24 months). The RFS nomogram

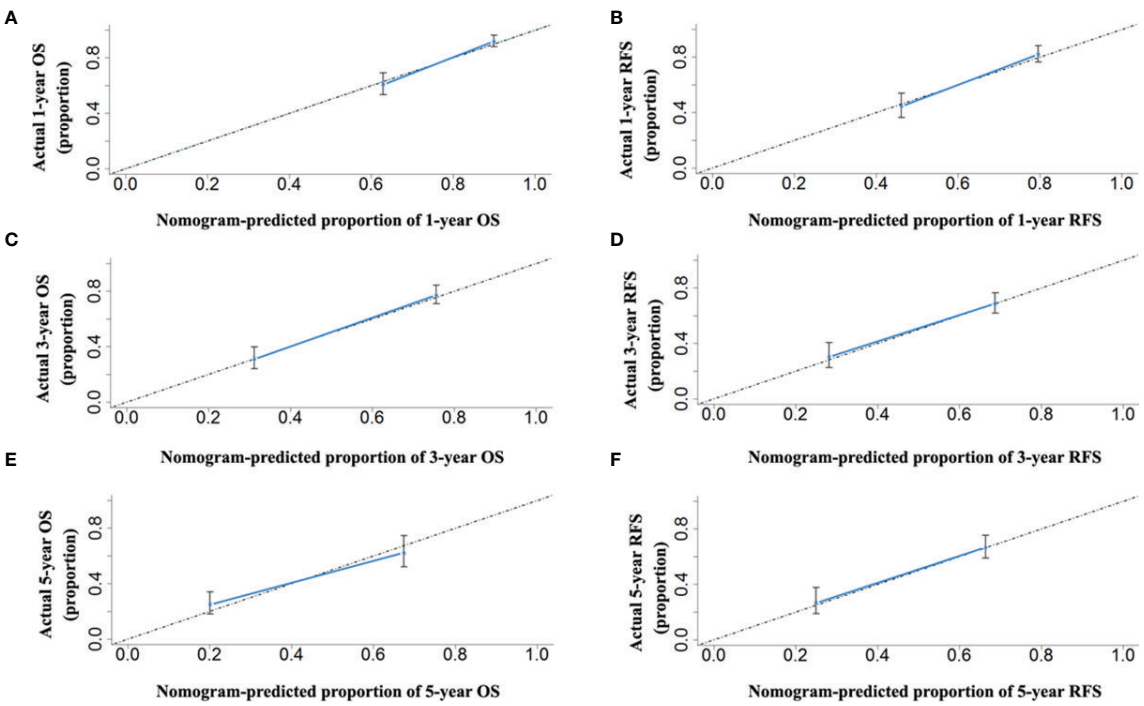

FIGURE 5 | The calibration curves for predicting the 1-, 3- and 5-year OS **(A, C, E)** and RFS **(B, D, F)** rates by nomogram prediction and actual observation in patients with HCC in the primary cohort.

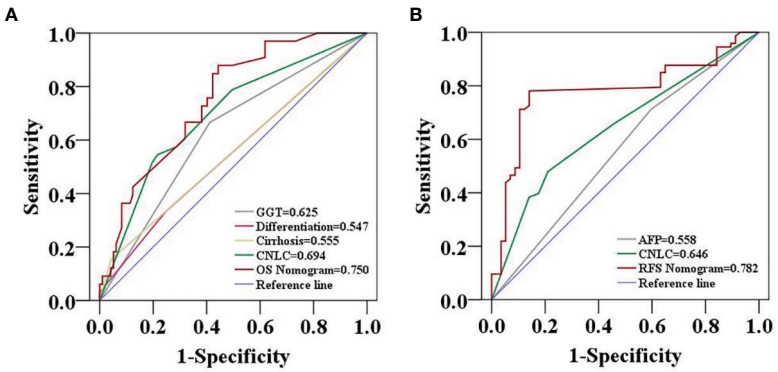

FIGURE 6 | Predictive accuracy comparison of each variable included in the OS **(A)** and RFS **(B)** nomograms by ROC curve analyses in the validation cohort. The ROC curves showed that the two nomograms were superior to the other variables in predictive accuracy.

could predict early recurrence very well. The C-indices were 0.699 (95% CI: 0.652–0.710). Of the 168 patients with ER, the proposed nomogram also performed well for OS prediction. The C-index was 0.707 (95% CI: 0.645–0.749). The calibration curves for the probability of both RFS in the 442 patients at 1 and 2 years (**Figures 8A, B**) and OS in the 168 patients with ER (**Figures 8C, D**) fit well and suggested that the two proposed nomograms could be applied for the prediction of the OS of HCC patients with ER.

DISCUSSION

Current unmet clinical needs for HCC patients involve accurate staging, prognosis, and treatment allocation. A variety of staging systems have been proposed to reflect the oncological prognosis and to guide treatment decisions (21–23). To date, no consensus has been achieved on which one is the most appropriate paradigm to accurately predict the patient's outcomes and to determine the appropriate intervention, particularly for surgical candidates with

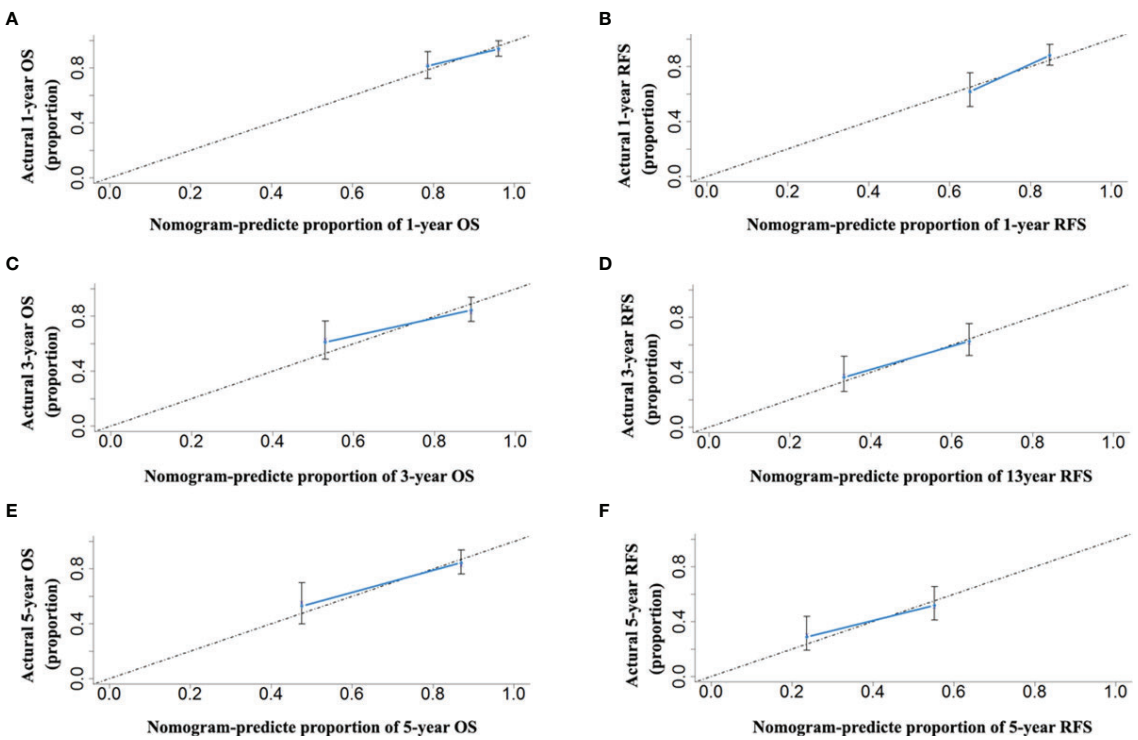

FIGURE 7 | The calibration curves for predicting the 1-, 3- and 5-year OS **(A, C, E)** and RFS **(B, D, F)** rates by nomogram prediction and actual observation in patients with HCC in the validation cohort.

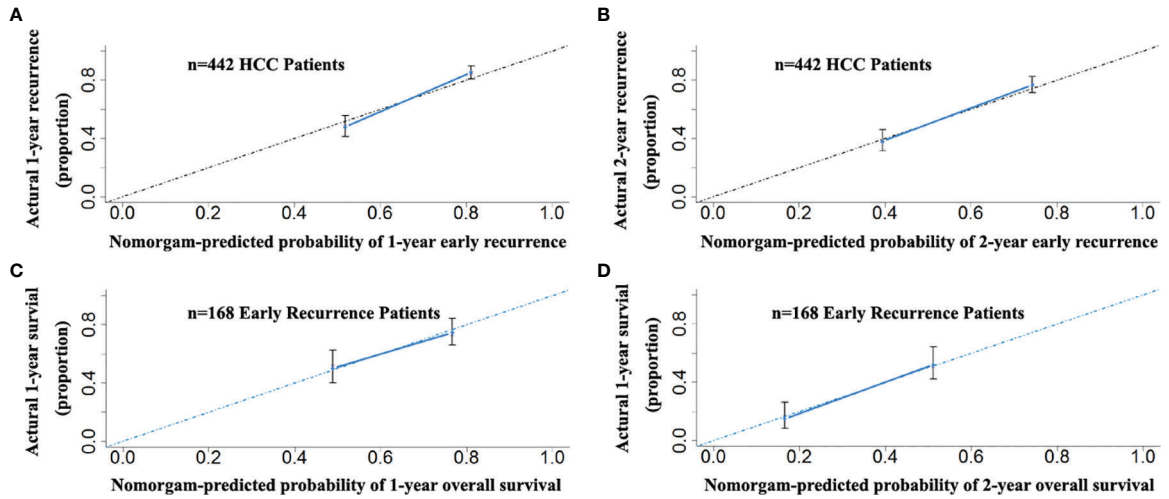

FIGURE 8 | The calibration curves for the probability of 1- and 2-year RFS nomogram showed good agreement between prediction and observation in the probability of early recurrence in the total of 442 patients with HCC **(A, B)**. The calibration curves for the probability of 1- and 2-year OS nomogram showed good agreement between prediction and observation in the probability of overall survival in 168 early recurrence patients with HCC **(C, D)**.

HCC (24). In this study, we identified and then compared the prognostic abilities of the CNLC with the BCLC and TNM staging systems, two commonly used staging systems, by ROC analysis and the C-index. Although the CNLC staging system performed better for HCC patients than the BCLC and TNM staging systems after curative resection, all three of them had a suboptimal prognostic performance (C-index<0.7), which suggested that some critical risk factors may not be included in these systems, and better paradigms with highly stable predictive accuracy for surgical HCC patients are needed. Different from many other nomograms constructed based on the combination of some molecules/genes and tumour characteristics, the main component of the nomograms, CNLC has been applicated widely in clinical practice, to a certain extent improving their reliabilities.

In addition to the CNLC staging system, the two nomograms integrated three independent risk factors for OS, including cirrhosis, GGT and tumor differentiation, and integrated AFP for predicting RFS. These risk factors have been identified previously for the surgical prognosis of HCC (25–30). First, the majority of HCC cases occur in a setting of cirrhosis, which constitutes an extremely heterogeneous inflammatory microenvironment and promotes the proliferation of premalignant cells and HCC development (29). Second, GGT can give rise to pro-oxidant reactions that can induce endogenous reactive oxygen species in tumor cells, which are involved in tumor formation, cell proliferation and apoptosis (26, 31, 32). Moreover, some inflammatory cytokines can induce the production of GGT, and GGT has prognostic effects on HCC development (26). Third, good differentiation to poor differentiation evolution is a critical phenomenon during HCC progression that is potentially related to the prognosis of HCC. In HCC tissues, poor tumor differentiation is significantly associated with reduced expression levels of the RCAN1 isoform 4, which acts as a suppressor of HCC through regulation of the calcineurin-nuclear factor of activated T cells pathway (33). Makiko's finding suggested that the switch of transferrin receptor (TFR) expression from TFR-2 to TFR-1, both iron metabolism-associated transmembrane transport iron protein receptors, is also related to HCC dedifferentiation (34). Fourth, AFP gene expression is associated with the carcinogenesis of HCC. Tumor relapse from intrahepatic metastasis or multicentric origin is accompanied by inconsistent serum AFP (35). On the other hand, high AFP levels are associated with a powerful tumor-host immune response (36) and increased invasive and metastatic abilities of tumor cells, one of the reasons for the high recurrence rate of HCC after surgery (37).

The OS and RFS nomograms might contribute to a significantly increased predictive accuracy due to incorporation of the CNLC staging system and several reliable independent risk factors. In this study, although the CNLC, BCLC and TNM staging systems had the ability to stratify patients after curative hepatectomy into different risk categories, the two nomograms seemed to have better predictive accuracy for survival and recurrence. Finally, ROC analysis, the C-index and the calibration curve showed that the OS and RFS nomograms integrating the CNLC staging system were superior to the CNLC staging system alone and better than the BCLC and TNM staging systems.

Clinically, it is still practically impossible to predict ER (≤ 24 months), which generally has a worse prognosis and is often considered to be the result of occult metastasis of the primary tumor (17). Our model is more powerful (C-index: 0.701, 0.659–0.739) for predicting HCC recurrence following curative hepatectomy than the BCLC and TNM staging systems. The RFS nomogram showed satisfactory predictive accuracy for recurrence within 2 years (ER) for all patients in the two cohorts. More interestingly, our findings highlight that the OS nomogram exhibited powerful predictive performance for patients with ER. The power of the prediction of the two nomograms was supported by the C-index and the calibration curve. These findings might shed light on an important association between the nature of the primary

tumor, such as tumor size, tumor number and vascular invasions, and the ER of HCC. Additionally, AFP may be an important gene associated with the dissemination of primary HCC tumor cells. Satellites nodules have already been identified as a risk factor of ER. However, this risk factor is not taken into consideration in this study due to lack of complete relevant information. Further investigation should be completed in the future.

We acknowledge that limitations exist in the present study (1). This was a retrospective study at a single institute. A trend toward significance indicates a need for large-scale multicenter studies for prospective verification. (2) Given the background HBV infection of most patients (86.4%, 382/442), the nomograms might not be suitable for HCC patients with etiologies other than HBV infection. (3) The CNLC staging system was established based on Chinese patients. Because the etiology and ethnic background of patients with HCC are diverse, these nomograms may not be suitable for a Western population mainly infected by HCV. (4) Although CNLC staging system has been applicated widely in Chinese HCC patients recently. But this nomogram may be further modified to improve its predictive accuracy and credibility.

In conclusion, the two nomograms improved the survival and recurrence predictive ability over the modified CNLC staging system. This information might be of more help for clinicians to thoroughly prepare HCC patients with potential early recurrence risks following surgery.

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 ethics review committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RL: funding acquisition, conceptualization, supervision, writing—review and editing. X-FW: data curation, formal analysis, funding acquisition, writing—original draft. PC: data curation, formal analysis, methodology, writing—original draft. K-LY and LL: formal analysis, methodology.

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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.2021.755920/full#supplementary-material

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REVIEW
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Liver-Directed Treatment Options Following Liver Tumor Recurrence: A Review of the Literature

Christopher T. Aquina[1,2], *Mariam F. Eskander*[1,3] *and Timothy M. Pawlik*[1*]

[1] Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, United States, [2] Digestive Health and Surgery Institute, AdventHealth Orlando, Orlando, FL, United States, [3] Division of Surgical Oncology, Department of Surgery, Robert Wood Johnson Medical School and Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, United States

Recurrence following curative-intent hepatectomy for colorectal cancer liver metastasis, hepatocellular carcinoma, or cholangiocarcinoma is unfortunately common with a reported incidence as high as 75%. Various treatment modalities can improve survival following disease recurrence. A review of the literature was performed using PubMed. In addition to systemic therapy, liver-directed treatment options for recurrent liver disease include repeat hepatectomy, salvage liver transplantation, radiofrequency or microwave ablation, intra-arterial therapy, and stereotactic body radiation therapy. Repeat resection can be consider for patients with limited recurrent disease that meets resection criteria, as this therapeutic approach can provide a survival benefit and is potentially curative in a subset of patients. Salvage liver transplantation for recurrent hepatocellular carcinoma is another option, which has been associated with a 5-year survival of 50%. Salvage transplantation may be an option in particular for patients who are not candidates for resection due to underlying liver dysfunction but meet criteria for transplantation. Ablation is another modality to treat patients who recur with smaller tumors and are not surgical candidates due to comorbidity, liver dysfunction, or tumor location. For patients with inoperable disease, transarterial chemoembolization, or radioembolization with Yttrium-90 are liver-directed intra-arterial therapy modalities with relatively low risks that can be utilized. Stereotactic body radiation therapy is another palliative treatment option that can provide a response and local tumor control for smaller tumors.

Keywords: recurrent liver tumors, hepatectomy, tumor ablation, liver transplant, transarterial chemoembolization (TACE), radioembolization of liver malignancies, SBRT (stereotactic body radiation therapy), recurrent liver tumors

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****Correspondence:***
Timothy M. Pawlik
tim.pawlik@osumc.edu

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide with the liver being the most common site of metastatic disease and primary liver cancer is the sixth most common cancer worldwide making the liver a very common site of disease (1). In fact, an estimated 149,500 patients in the United States will be diagnosed with colorectal cancer in 2021 among whom 25% will present with synchronous liver

metastasis and 50% will eventually develop metachronous liver metastasis; in addition, an estimated 42,230 patients in the United States will be diagnosed with liver or intrahepatic bile duct malignancy in 2021 (2–4). Among these patients, approximately 10-20% of individuals with colorectal cancer liver metastasis (CRCLM), 20% of patients with hepatocellular carcinoma (HCC), and 50% of those with intrahepatic cholangiocarcinoma will undergo resection with curative intent (5–7). Unfortunately, recurrence rates are as high as 70% for each of these cancer types (8–10). We herein review currently available therapeutic modalities and outcomes associated with liver-directed treatment of patients with hepatic tumor recurrence.

METHODS

MEDLINE, PubMed and Web of Science databases were queried for published articles through August 31st, 2021 using the search terms *recurrence* AND {[(*colon*, *rectal*, *colorectal)* AND *(cancer, neoplasm, adenocarcinoma)* AND *liver metastasis*] OR *hepatocellular carcinoma* OR *cholangiocarcinoma*}. The results were reviewed to identify English language primary studies that investigated outcomes following re-intervention for liver recurrence following prior resection of colorectal cancer liver metastasis, hepatocellular carcinoma, or cholangiocarcinoma. Specific re-interventions included repeat hepatectomy, liver transplantation, radiofrequency (RFA) or microwave ablation (MWA), hepatic artery infusion chemotherapy, transarterial embolization, chemoembolization, radioembolization, and stereotactic body radiation therapy (SBRT). References embedded in publications were also reviewed to identify additional studies.

TREATMENT OF RECURRENT LIVER TUMORS

Colorectal Cancer Liver Metastasis (CRLM)

While 10-year overall survival can be as high as 20-30% following hepatectomy for colorectal cancer, up to 70% of patients will develop disease recurrence (8, 11). Factors associated with recurrence include a node-positive primary tumor, >3 liver metastases, and a liver metastatic lesion >4 cm (12). Among patients who develop recurrent disease following initial curative-intent treatment of CRLM, an estimated 43% develop liver-only recurrence, 35% have extrahepatic only disease, and 21% experience both intra- and extrahepatic recurrence (13). Among patients with suspected recurrence, the work-up should include clinical examination, liver and renal functional tests, serum carcinoembryonic antigen (CEA) level, and imaging consisting of computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis (14, 15). Additional evaluation of the chest with CT scan is also mandatory.

Individuals with liver-only recurrence may be candidates for curative-intent resection and/or ablation. For patients who also have evidence of extrahepatic disease recurrence, systemic therapy +/- liver-directed therapy is warranted. Current first-line systemic therapy options include 5-fluorouracil or capecitabine in combination with oxaliplatin (FOLFOX or CAPEOX), irinotecan (FOLFIRI), or both agents (FOLFOXIRI) with the potential addition of a targeted agent (e.g., bevacizumab for *RAS* mutated tumors; cetuximab or panitumumab for *RAS* wild-type tumors). Among patients with deficient DNA mismatch repair and microsatellite instability (dMMR/MSI-H), the addition of checkpoint inhibitors (pembrolizumab, nivolumab, or ipilimumab) may be warranted (14, 15). In addition to systemic therapy, liver-directed treatment modalities include hepatic artery infusion pump therapy, arterial-directed embolic therapy, and SBRT.

Careful assessment of liver functional reserve prior to any liver-directed therapy is essential. For patients being considered for repeat hepatectomy, assessment for an adequate future liver remnant using CT or MRI volumetry is required to limit the risk of postoperative liver failure (16). In general, the future liver remnant (FLR) is adequate when the FLR is ≥ 20% of the total liver volume (TLV) in patients with a normal liver, ≥ 30% in patients who received chemotherapy, and ≥ 40% in those with hepatic fibrosis or cirrhosis (17). For patients in which there is a concern for an inadequate future liver remnant, preoperative portal vein embolization may be an option to induce hypertrophy of the anticipated future liver remnant (18). Another option is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). However, the reported mortality rate after ALPPS and resection of CRCLM was 9% raising concern about its safety (19). For patients with cirrhosis or suspected liver dysfunction, a history of gastrointestinal hemorrhage, ascites, encephalopathy, or thrombocytopenia with platelet count < 150,000/μL will impact risk of hepatectomy. The Child-Turcotte-Pugh Classification, which is calculated based on the degree of encephalopathy and ascites and measurements of serum bilirubin, serum albumin, and prothrombin time or international normalized ratio, should be estimated as resection is usually reserved for Class A and carefully selected Class B patients with cirrhosis due to increased risk of postoperative morbidity and mortality. Furthermore, portal hypertension should be assessed through endoscopy to evaluate for esophageal varices, as well as imaging to assess for ascites, splenomegaly, liver nodularity, portosystemic collaterals, and mesenteric vein thrombosis. If the diagnosis of portal hypertension is still in question following these less invasive diagnostic modalities, percutaneous or transjugular liver biopsy or hepatic venous pressure gradient (HVPG) measurement can be performed. A HVPG ≥ 6 mmHg indicates portal hypertension and a HVPG ≥ 10 mmHg has been associated with clinically significant portal hypertension and increased post-operative risk.

Repeat Hepatectomy

Repeat resection has been demonstrated to be a safe and effective treatment for recurrent CRLM. While reoperation can be challenging due to abdominal and perihepatic adhesions and altered hepatobiliary anatomy, postoperative 30-day mortality is less than 2%, and there is no difference in morbidity and mortality compared with initial liver resection for CRLM (20–22). In addition, a laparoscopic approach for repeat hepatectomy

appears safe and may provide an advantage over open resection with one meta-analysis demonstrating lower intraoperative blood loss, less overall and major postoperative complications, shorter hospital stay, a higher R0 resection rate, and equivalent operative time, transfusion rate, and mortality (23). While there are no randomized controlled trials comparing resection to other treatment modalities for recurrent disease, hepatectomy remains the gold standard treatment modality for resectable recurrent CRLM.

In carefully selected patients, long-term survival with potential cure can be achieved with resection of recurrent liver disease. Across a multitude of single-institution retrospective studies, the reported 5-year overall survival following repeat hepatectomy for liver-only recurrence ranges from 27% to 67% (**Table 1**) (24–37). However, survival appears to be shorter after each subsequent liver resection for recurrence. In a study by de Jong et al. that included 246 patients with CRLM who underwent curative intent surgery with resection alone, RFA alone, or a combination of resection and RFA, 5-year overall survival was 47%, 33%, and 24% following the first, second, and third curative intent operations, respectively (21). As with any patient under consideration for a hepatectomy, preoperative assessment of patient performance status and adequate remnant liver volume is essential.

Prognostic factors associated with increased risk of recurrence or worse survival following repeat hepatectomy are a history of synchronous liver metastasis, an initial CRLM ≥5 cm, positive surgical margins at initial resection, a relapse-free interval of less than one year, the presence of multiple liver lesions or extrahepatic disease at the time of second hepatectomy, and positive surgical margins at repeat hepatectomy (27, 36, 38, 39). Limited evidence is available regarding the benefit of perioperative systemic therapy in patients who undergo repeat resection. However, the European Organization for Research and Treatment of Cancer (EORTC) intergroup trial 40983 demonstrated a progression-free survival benefit, but there was no overall survival benefit among patients who received perioperative FOLFOX4 compared with surgery alone for resectable CRLM (40).

Tumor Ablation

Tumor ablation in the form of RFA or MWA is a locoregional treatment that can be utilized alone or in combination with resection with curative or palliative intent. It appears to be an effective and safe treatment modality in patients with CRLM ≤ 3 cm in diameter who are otherwise not good candidates for resection due to unfavorable tumor location, comorbidity burden, or functional status (41). While there are no randomized controlled trials that have assessed differences in outcomes between ablation and repeat hepatectomy, there are several recent retrospective studies available comparing short-term morbidity and survival between the two treatment modalities.

In a single-institution retrospective study of 64 consecutive patients in the United Kingdom who developed liver-limited recurrence following hepatectomy between 2010 and 2015, 33 patients were treated with RFA or MWA, and 31 patients were treated with repeat hepatectomy (42). Overall morbidity (12.1% vs 38.7%, p=0.02) and length of stay (1 vs 5 days, p<0.001) were significantly lower in the ablation group. After a median follow-up of 36.2 months across the study cohort, median overall survival was the same between the two groups at 33.3 months (p=0.45). However, median progression-free survival was longer (10.2 vs 4.3 months, p=0.002) among patients in the repeat resection group. Given the lower morbidity rate, yet shorter progression-free survival associated with ablation, the authors concluded that the choice between ablation and resection should be made on a personalized basis. In another single-institution retrospective study in China that included 194 patients with recurrent CRLM, 50 patients underwent repeat liver resection, and 144 patients underwent RFA (43). Indications for RFA included ≤3 tumors with a maximum diameter of ≤5 cm or >4 tumors with a maximum diameter of ≤3 cm. In propensity-matched analyses, there was no significant difference in complication rates, disease-free survival, or overall survival. However, postoperative length of stay (14.5 vs 10.6 days, p=0.006) was longer in the hepatic resection group. Similar results were observed in a retrospective study utilizing the Amsterdam Colorectal Liver Met Registry. Among 136 patients, 100 individuals were treated with repeat

TABLE 1 | Survival after repeat resection for colorectal cancer liver metastasis recurrence in the liver.

Authors	Years	Type	N	Median OS (months)	1-year OS	3-year OS	5-year OS
Adam et al. (24)	1984-2000	Single center	199	–	88%	54%	35%
Ahmad et al. (25)	1997-2003	Single center	19	48	95%	79%	44%
Battula et al. (26)	1998-2011	Single center	53	45	85%	61%	52%
Ishiguro et al. (27)	1985-2004	Single center	111	43	91%	74%	41%
Maeda et al. (28)	2000-2016	Single center	17	>60	–	–	52%
Nanji et al. (29)	2002-2009	Multicenter	78	45	–	–	45%
Park et al. (30)	2003-2016	Single center	70	62	–	62%	50%
Sa Cunha et al. (31)	1985-2000	Single center	40	32	–	55%	31%
Saiura et al. (32)	1999-2008	Single center	73	NR	–	75%	67%
Shaw et al. (33)	1987-2005	Single center	66	56	94%	68%	44%
Thelen et al. (34)	1988-2006	Single center	94	–	89%	55%	38%
von Heesen et al. (35)	2001-2006	Single center	23	–	–	66%	27%
Yamamoto et al. (36)	1985-1997	Single center	75	30	–	48%	31%
Yamazaki et al. (37)	2004-2011	Single center	37	–	92%	52%	36%

Includes studies with ≥10 patients who underwent repeat resection.
OS, overall survival following second hepatectomy; NR, not reached.

thermal ablation and 36 underwent repeat liver resection between May 2002 and December 2020. There were no significant difference in overall survival, distant progression-free survival, local tumor progression-free survival, or complications between the two groups. However, mean length of stay was significantly shorter among patients in the thermal ablation group (2.1 vs 4.8 days, p=0.009). While these retrospective studies suggest that repeat ablation for recurrent CRCLM ≤ 3 cm in diameter is equivalent to repeat hepatectomy with respect to survival and appears to be associated with lower morbidity, the awaited phase III randomized controlled COLLISION trial comparing 5-year survival between these two groups should provide more definitive evidence (44).

Hepatic Arterial Infusion Pump Chemotherapy

Hepatic arterial infusion pump (HAIP) chemotherapy with floxuridine has been shown to have CRLM response rates as high as 92%, conversion-to-resection rates as high as 47% for initially unresectable CRLM, and improvement in 2-year hepatic disease-free survival from 60% to 90% in clinical trials (45–47). Therefore, HAIP chemotherapy may be an effective treatment modality for patients with initially unresectable recurrent CRLM or as adjuvant therapy to reduce the risk of liver re-recurrence by treating residual liver micrometastases. In the only study to investigate outcomes following HAIP chemotherapy for recurrent CRCLM, Buisman et al. performed a retrospective cohort study of 374 patients with liver-only disease who underwent ablation and/or resection of recurrent CRLM (48). A total of 81 patients were treated with HAIP chemotherapy for a maximum of 6 cycles; patients who received HAIP chemotherapy were significantly more likely to be < 70 years old at the time of the index CRLM, to be female, to have had positive primary tumor nodal status, and to have received perioperative systemic chemotherapy (p<0.05). Despite differences between the two groups, adjuvant HAIP chemotherapy was independently associated with improved hepatic disease-free survival (hazard ratio [HR]=0.60, 95% confidence interval [CI]=0.38-0.93, p=0.02) and overall survival (HR=0.59, 95% CI=0.38-0.92, p=0.02) compared with patients who did not receive adjuvant HAIP chemotherapy. While these results are promising, there are currently no randomized controlled trial data with respect to HAIP chemotherapy for recurrent CRCLM.

Arterially Directed Embolic Therapy

Transarterial chemoembolization (TACE) is a minimally invasive treatment option for patients with unresectable CRCLM that is relatively well-tolerated and may provide a survival benefit, as well as facilitate conversion to resectability through local delivery of high-dose chemotherapy followed by arterial occlusion. While no study investigating its oncologic benefit for recurrent CRLM was identified, two small randomized trials have investigated the effect of TACE with drug-eluting beads preloaded with irinotecan (DEBIRI) on initial CRLM (49, 50). In a multi-institutional phase III trial by Fiorentini et al, 74 patients with unresectable CRLM who no radiological evidence of extrahepatic disease were randomized to receive DEBIRI or systemic chemotherapy with FOLFIRI; the DEBIRI group had longer median overall survival (22 vs 15 months, p=0.03), longer progression-free survival (7 vs 4 months, p=0.006), and longer median duration of improved quality of life (8 vs 3 months, p=0.00002) (49). In another multi-institutional phase III trial by Martin et al, 60 patients who were chemotherapy-naïve with liver dominant disease defined as ≥80% of the tumor burden confined to the liver were randomized to modified FOLFOX, bevacizumab, and DEBIRI (mFOLFOX-DEBIRI) or systemic therapy alone with modified FOLFOX and bevacizumab (mFOLFOX) (50). The mFOLFOX-DEBIRI group had a higher overall response rate at 2 months (78% vs 54%, p=0.02) and a higher rate of conversion to resectability (35% vs 16%) compared with mFOLFOX alone.

Another local treatment option for unresectable CRLM refractory to systemic chemotherapy is selective internal radiotherapy in which yttrium-90 (^{90}Y)-tagged glass or resin microspheres are selectively delivered to the tumor *via* the hepatic artery and provide high doses of radiation. ^{90}Y is typically well-tolerated with fatigue, nausea, and vomiting being the most common side effects (51). While there are limited data regarding its efficacy for patients who underwent prior resection of CRLM, one large multicenter observational study by Hickey at al included 531 patients who underwent ^{90}Y radioembolization of CRLM of which 98 patients had undergone prior resection (52). Median overall survival for the entire study cohort from the time of first ^{90}Y treatment was 10.6 months with a longer survival benefit observed among individuals without extrahepatic disease (14.4 vs 6.6 months, p<0.001). ^{90}Y radioembolization may also allow for conversion to resection with a conversion rate as high as 29% in one small study that included 14 patients with CRCLM (53).

Stereotactic Body Radiation Therapy (SBRT)

SBRT allows for higher doses of radiation over fewer treatment fractions and has demonstrated good local control of CRLM with low toxicity in small studies (54). In a single institution retrospective observational study by Viganò et al. that included 206 consecutive patients with recurrent CRLM who had undergone liver resection between 2004 and 2013, local disease control and overall survival were compared among patients who underwent repeat resection, RFA, or SBRT (55). Among 14 patients who underwent SBRT, the 2-year local disease control rate was 70.8% versus 90.9% for repeat liver resection (p=0.051) and 56.4% for RFA (p=0.536). While larger prospective studies are needed, SBRT can be considered in patients with unresectable liver-limited disease at centers with expertise.

Salvage Liver Transplantation (SLT)

Liver transplantation for unresectable CRCLM remains controversial due to the risk of high recurrence with a 1-year disease-free survival rate of only 39% (56). However, in areas where organ scarcity is not an issue, it may provide an overall survival benefit versus systemic therapy alone (estimated 5-year overall survival only 10%) (57). In the SECA-1 trial that included 21 patients who underwent liver transplantation for unresectable CRCLM, time from primary tumor resection to liver

transplantation > 2 years, treatment response or stable disease following chemotherapy, pre-transplantation serum CEA < 80 μg/L, and tumor diameter < 5.5 cm were associated with more favorable survival outcomes (58). In the SECA-1 (N=4) and subsequent SECA-2 (N=4) trials, only 8 patients with recurrent CRCLM following prior liver resection were included in the studies. Furthermore, stratified outcome data by recurrence status were not reported (58, 59). Given the overall paucity of data regarding liver transplantation for CRCLM and its association with high recurrence rates in the small studies that have been published, SLT should only be performed for recurrent CRCLM as part of a comprehensive transplant program after extensive multi-disciplinary review.

Hepatocellular Carcinoma (HCC)

For patients without cirrhosis and significant comorbidity burden, hepatectomy is often the treatment modality of choice for resectable HCC. In contrast, for patients with cirrhosis meeting the Milan criteria of a solitary tumor ≤ 5 cm in diameter or no more than three tumor nodules all measuring ≤ 3 cm in diameter without major vessel or extrahepatic involvement, liver transplantation is the treatment of choice (60). Recurrence rates have been reported to be as high as 70% following hepatectomy and 18% following liver transplantation, which are most often detected on surveillance multiphasic CT or MRI of the liver (9, 61). Following liver resection, most recurrences occur early with approximately 75% occurring within 2 years, and approximately 90% of recurrences occurring in the remnant liver (62). Recurrence patterns following liver transplantation differ from that of initial partial hepatectomy. While most recurrences also occur early with a median time to recurrence of 12 months, 23% develop liver-only recurrence, 39% develop both intra- and extrahepatic recurrence, and 39% develop isolated extrahepatic recurrence (61). For patients with suspected recurrence, work-up should include clinical examination, liver and renal functional tests, serum alpha-fetoprotein (AFP) level, and imaging consisting of multiphasic liver protocol CT abdomen/pelvis or intravenous contrast-enhanced MRI abdomen/pelvis, CT chest, and bone scan in the setting of skeletal symptoms (63).

Patients with liver-only recurrence may be candidates for curative-intent repeat hepatectomy, liver transplantation, or ablation. For individuals with unresectable disease, other liver-directed therapy modalities include TACE, ^{90}Y, and SBRT. For patients who also have evidence of extrahepatic disease recurrence, enrollment in a clinical trial or systemic therapy with atezolizumab + bevacizumab or a tyrosine kinase inhibitor such as sorafenib or lenvatinib may be warranted (63).

Given the high prevalence of cirrhosis in patients with HCC, a full assessment of underlying liver function and portal hypertension prior to any intervention is especially important. While there are no published algorithms regarding liver function, tumor stage, and first-line treatment recommendations for recurrent HCC, the Barcelona Clinic Liver Cancer and Japan Society of Hepatology treatment strategy algorithms can be extrapolated and utilized as treatment guides (64, 65). In general, resection is an option only in patients with Child-Pugh Class A cirrhosis or highly selected patients with Child-Pugh B cirrhosis without evidence of portal hypertension who have a FLR : TLV ratio ≥ 40% on CT or MRI volumetry. Liver transplantation should be considered in patients with an inadequate FLR who would not be a candidate for repeat hepatectomy. Ablation can be considered in patients with portal hypertension who have small (<3-5 cm) lesions. Hepatectomy, ablation, TACE, ^{90}Y, SBRT, and systemic therapy are generally contraindicated in patients with Child-Pugh Class C cirrhosis; salvage liver transplantation may be the only option in those individuals who meet transplant criteria and have acceptable functional status.

Repeat Hepatectomy

Repeat hepatectomy for recurrent HCC is safe with comparable complication rates to initial hepatectomy and is often the curative-intent treatment of choice (66). While patients who develop recurrent HCC following liver transplantation have a worse prognosis versus patients who undergo partial hepatectomy with a median overall survival after recurrence of 10-13 months versus 24 months, hepatectomy is also the treatment of choice in post-transplant patients (67). As most patients with HCC have underlying liver disease, assessment of preoperative liver function, identification of portal hypertension, and determination of an adequate functional liver remnant are key in appropriate patient selection to limit the risk of postoperative morbidity. In addition, for patients who underwent initial partial hepatectomy, consideration should be given to the time interval from initial resection to recurrence. Early recurrences within one year appear to arise from intrahepatic metastasis from the primary tumor and are associated with a poor prognosis; in contrast, recurrences beyond one year are more likely to be multicentric occurrences arising in the setting of chronic liver disease that are associated with a better prognosis (68–70). Given that early recurrence is typically associated with unfavorable tumor biology including microvascular invasion, satellite micrometastases, and lower response rates to potentially-curative treatment such as repeat hepatectomy, tumor ablation, and salvage liver transplantation (SLT), initial treatment with less morbid therapy, such as TACE or combined therapy with TACE and RFA or a tyrosine kinase inhibitor, should be considered in these patients (68, 71).

Retrospective studies have demonstrated that partial hepatectomy can lead to long-term survival in appropriately selected patients following both initial hepatectomy and liver transplantation. Five-year overall survival range from 22% to 73% following repeat resection for recurrent HCC in the liver and 31% to 35% following metastasectomy for recurrent HCC following liver transplantation (**Table 2**) (66, 72–85). However, the main limitation of repeat resection is that only 15% to 30% of patients are eligible for repeat hepatectomy due to an inadequate future liver remnant, cirrhosis, multifocal disease, or gross vascular invasion (71).

In a systematic review of 22 observational studies, prognostic factors associated with increased risk of recurrence or worse survival following repeat hepatectomy were tumor size ≥ 3 cm, multifocal disease, micro- and macrovascular invasion, relapse-free interval of less than one year, cirrhosis, and receipt of a blood transfusion (86).

TABLE 2 | Survival after resection for hepatocellular carcinoma (HCC) recurrence in the liver.

Authors	Years	Type	N	Median OS (months)	1-year OS	3-year OS	5-year OS
***After initial partial hepatectomy for primary HCC**							
Ho et al. (72)	2001-2007	Single center	54	–	–	–	72%
Huang et al. (73)	1995-2010	Single center	82	–	71%	41%	22%
Itamoto et al. (74)	1990-2004	Single center	84	–	88%	67%	50%
Li et al. (75)	1997-2015	Single center	103	65	92%	–	54%
Lu et al. (76)	2004-2015	Single center	138	–	92%	82%	73%
Midorikawa et al. (77)	2000-2017	Single center	273	68	–	–	58%
Minagawa et al. (78)	1994-2000	Single center	67	–	93%	70%	56%
Sun et al. (79)	1997-2003	Single center	57	–	70%	61%	31%
Wang et al. (80)	2004-2010	Single center	128	–	98%	84%	64%
Wu et al. (66)	1990-2007	Single center	149	–	–	–	56%
†After initial liver transplantation for primary HCC							
Bodzin et al. (81)	1984-2014	Single center	25	28	–	–	–
Fernandez-Sevilla et al. (82)	1991-2013	Single center	22	35	–	–	–
Huang et al. (83)	1997-2012	Single center	15	–	92%	51%	35%
Regalia et al. (84)	1987-1996	Multicenter	7	–	–	57%	–
‡Sapisochin et al. (85)	2000-2012	Multicenter	38	–	75%	60%	31%

**Includes studies with ≥50 patients who underwent repeat resection.*
†Includes resection of extrahepatic metastases.
‡Includes resection and ablation.
OS, overall survival following hepatectomy for recurrent HCC.

Shorter time to recurrence was significant in 89% of the studies that reported time to recurrence. As mentioned, early recurrence is strongly associated with intrahepatic metastasis from the primary tumor and unfavorable tumor biology. Therefore, less aggressive initial therapy for recurrent HCC is warranted in most of these patients. For patients who underwent initial liver transplantation, unfavorable prognostic factors following metastasectomy for recurrent HCC include pretransplant model for end-stage liver disease (MELD) score > 23, elevated pretransplant neutrophil-to-lymphocyte ratio, microvascular invasion in the explanted liver, shorter time to recurrence, AFP level > 100 ng/mL, intrahepatic recurrence, and multifocal recurrence (81, 82, 85).

Salvage Liver Transplantation (SLT)

Since the first report of SLT for recurrent HCC by Majno et al. in 2000, subsequent studies have demonstrated the feasibility of liver transplantation for intrahepatic HCC recurrence following partial hepatectomy (87, 88). Five-year overall survival of 42% to 73% and 5-year recurrence-free survival rates of 32% to 81% following SLT for recurrent HCC have been reported across various retrospective and prospective studies (89–95). While there are no randomized controlled trials comparing repeat resection to SLT, numerous observational studies and several meta-analyses have been performed. For example, in a meta-analysis by Wang et al. that included 840 patients across 7 retrospective studies, SLT had improved 3-year (odds ratio [OR]=3.23, 95% CI=1.45-7.20, p=0.004) and 5-year disease-free survival (OR=4.79, 95% CI=1.88-12.25, p=0.001) compared with repeat hepatectomy; however, there was no difference in overall survival between the two groups (96). Similarly, in a meta-analysis by Kostakis et al. that included 516 patients across 3 prospective and 4 retrospective studies, SLT was associated with longer disease-free survival (HR=0.42, 95% CI=0.25-0.70, p=0.0009) compared with repeat liver resection; in addition, there was no difference in postoperative mortality or overall survival between the two groups (97). However, SLT was associated with worse short-term outcomes compared with repeat hepatectomy including higher blood loss, longer operative time, longer length of stay, and higher postoperative morbidity. In a different meta-analysis by Zheng et al. that included 2,818 patients from 21 retrospective studies, the authors compared overall and recurrence-free survival between SLT, repeat hepatectomy, RFA, TACE, and SBRT and ranked the modalities (98). With respect to overall survival, the ranking from most benefit to least benefit was SLT, repeat hepatectomy, SBRT, RFA, and TACE. SLT had significantly better recurrence-free survival compared with each of the treatment modalities. However, similar to the other meta-analyses, there was no significant difference in overall survival between repeat hepatectomy and SLT.

While there are not currently any official guidelines regarding SLT in the setting of recurrent HCC, various liver transplantation criteria, such as Milan or University of California San Francisco (UCSF) criteria, are typically applied by different institutions to identify candidates for SLT (60, 99). Given the scarcity of organs, repeat resection is preferred for patients with resectable intrahepatic disease and adequate liver function with SLT being reserved for patients who develop cirrhosis after hepatectomy for the primary HCC or who have unresectable disease but meet liver transplantation criteria. Ideally, SLT should be limited to patients with recurrent HCC who meet the stricter Milan criteria or carefully selected patients who meet the UCSF criteria, without microvascular invasion, and within 6 months of HCC recurrence (71).

Tumor Ablation

Compared with repeat hepatectomy and SLT, RFA and MWA are minimally invasive procedures with generally much lower morbidity, have lower rates of post-procedure liver dysfunction, and can be performed on a repeat basis (71, 100). Furthermore,

in appropriately selected patients with smaller tumors, 5-year overall survival of 26% to 71% can be achieved (72, 76, 80, 83, 101–105). Ablation can also be utilized for bridging or downstaging to transplant (106). However, 5-year recurrence-free survival is lower with rates ranging from 0% to 30% across studies (80, 83, 101, 103, 104). While MWA has become the preferred modality at many institutions due to faster ablation times, less susceptibility to heat-sink effect, and the ability to perform multiple ablations simultaneously compared with RFA, MWA and RFA. These ablative modalities appear to have similar recurrence rates and overall survival in the treatment of primary HCC (107).

There is currently only one randomized controlled trial comparing repeat hepatectomy to RFA for recurrent HCC. Xia et al. randomized 240 patients with early-stage recurrent HCC defined as a solitary lesion ≤ 5 cm in diameter or ≤3 nodules each measuring ≤ 3 cm in diameter without evidence of macroscopic vascular invasion or extrahepatic metastases to either repeat hepatectomy or percutaneous RFA (108). There were no significant differences in outcomes between the repeat hepatectomy and RFA groups with respect to median overall survival (47.1 vs 37.5 months, p=0.17), 5-year overall survival (43.6% vs 38.5%, p=0.29), median recurrence-free survival (38.9 vs 25.8 months, p=0.09), and 5-year recurrence-free survival (36.2% vs 30.2%, p=0.09). However, in subgroup analysis of patients with a nodule > 3 cm in diameter, repeat hepatectomy was associated with improved overall survival (HR=0.55) and recurrence-free survival (HR=0.66) versus RFA. Therefore, repeat resection may be associated with better local disease control for larger tumors > 3 cm in diameter; RFA, however, had similar efficacy to repeat hepatectomy for smaller tumors measuring ≤ 3 cm in diameter. While these findings suggest that repeat hepatectomy and ablation may have equivalent efficacy for recurrent tumors ≤ 3 cm, additional studies comparing outcomes between repeat hepatectomy and ablation stratified by the number and size of recurrent tumors may better clarify the optimal therapeutic approach.

Arterially Directed Embolic Therapy

TACE is the most common treatment modality utilized for recurrent HCC following initial resection (71). However, there can be a significant risk of worsened liver dysfunction following the procedure among patients with underlying cirrhosis who have undergone prior hepatectomy. To help prevent Child-Pugh grade deterioration, the up-to-seven criteria, which is defined as the sum of the diameter of the largest tumor and the number of tumors, or the Mac-2 binding protein glycosylation isomer (M2BpGi) biomarker to assess liver fibrosis can be utilized to identify patients who are less likely to tolerate TACE (71, 109, 110). While TACE has been demonstrated to be inferior to repeat hepatectomy and SLT, it can improve survival among patients with early recurrence or multifocal disease with 5-year overall survival of 12% to 56% (66, 72, 77, 80, 98, 111–113). Similar to ablation, TACE can also be utilized for bridging or downstaging to transplant (106). While bland transarterial embolization (TAE) also has been demonstrated to be safe and effective for recurrent HCC, most studies have investigated the efficacy of TACE as arterially directed embolic therapy, and conventional TACE is the only transarterial modality found in randomized trials to provide a survival benefit compared with supportive care alone in patients with unresectable HCC not amenable to liver transplantation or ablation (114, 115). Therefore, TACE is generally the preferred treatment modality.

Selective internal radiotherapy with ^{90}Y appears to be a safe alternative treatment option to TACE, especially in patients who are not candidates for TACE due to portal vein thrombosis (106, 116). It also appears to have similar efficacy to TACE (71). However, data are currently lacking with respect to outcomes following the use of ^{90}Y for recurrent HCC following initial liver resection.

Stereotactic Body Radiation Therapy (SBRT)

SBRT can be utilized in patients with Child-Pugh Class A or early Class B cirrhosis with adequate liver volume outside of the radiation field. However, it should be avoided in patients with Child-Pugh score ≥ 8 due to increased risk of radiation-induced hepatic toxicity unless it is being utilized in the context of a clinical trial or as a bridge to SLT (117). While there are limited data regarding SBRT for recurrent intrahepatic HCC, a retrospective study by Shen et al. reported favorable outcomes following SBRT (118). Among 30 patients who underwent SBRT for recurrent HCC between 2008 and 2017, median overall survival was 50 months, the 1-year overall survival was 78% and 3-year overall survival was 58%. The authors performed a propensity score matching analysis comparing outcomes between 22 patients who underwent SBRT and 37 patients who underwent TACE and observed that SBRT was associated with improved 1-year overall survival (73% vs 38%, p=0.003) and 3-year overall survival (67% vs 0%, p < 0.001) versus TACE. There are also reports that SBRT can safely and effectively utilized as a bridge to transplantation for HCC (119, 120). In addition, repeat SBRT appears feasible with minimal toxicity in the setting of HCC recurrence following an initial course of SBRT (121). While these results are promising, prospective studies are needed.

Cholangiocarcinoma

The liver is the most common site of recurrence after resection of intrahepatic cholangiocarcinoma (iCCA) (122). In a large German series of 202 patients with resected iCCA, 60.9% had a recurrence at a median of 7.5 months after resection, and 44% recurred in the liver only (123). In another Italian series of the 140 patients who underwent surgery for iCCA, 58.2% of the patients who recurred had liver metastasis (124). While hepatic recurrence is also common in hilar and distal cholangiocarcinoma, repeat resection is rarely possible (125). Therefore, most data on treatment of recurrent intrahepatic disease related to cholangiocarcinoma has focused on iCCA. Unfortunately, there is a paucity of prospective data to guide treatment decisions for intrahepatic recurrence.

Among patients with suspected intrahepatic recurrence, the work-up should include clinical examination, liver and renal functional tests, serum CEA level, serum CA 19-9 level, and imaging consisting of multiphasic CT or MRI of the chest,

abdomen, and pelvis. Individuals with unifocal recurrence and no evidence of extrahepatic disease may be candidates for curative-intent resection and/or ablation. For patients who also have evidence of extrahepatic disease recurrence, systemic therapy is warranted. The currently preferred multi-agent regimen is gemcitabine and cisplatin, but other first-line options include 5-fluorouracil or capecitabine and a platinum-based agent consisting of oxaliplatin or cisplatin, gemcitabine and albumin-bound paclitaxel, capecitabine, or oxaliplatin, and single-agent therapy with 5-fluorouracil, capecitabine, or gemcitabine. Targeted therapy with entrectinib or larotrectinib can be considered in patients with NTRK gene fusion-positive tumors, and pembrolizumab can be considered in patients with MSI-H/dMMR tumors (63).

For patients being considered for liver-directed therapy, liver function should be assessed, and CT or MRI volumetry should be obtained for repeat hepatectomy candidates. For patients in which there is a concern for an inadequate future liver remnant, preoperative portal vein embolization should be considered. ALPPS should be avoided as it is associated with a mortality rate as high as 27% for cholangiocarcinoma (19).

Repeat Hepatectomy

Few studies, all retrospective, have examined survival outcomes following repeat liver resection, and the results have been overall favorable for highly selected patients. Patients who have a repeat resection survive longer than patients who do not undergo surgery (126). Compared with chemotherapy or other local therapies, surgery has been associated with improved survival outcomes (127). In a multicenter analysis, patients who underwent repeat liver resection had longer median survival (26.1 months) versus individuals who underwent ablation (25.5 months) or intra-arterial therapies (9.6 months) ($p = 0.01$) (10). Bartsch et al. reported no difference in survival among patients who were re-resected versus patients who had no recurrence at all (127). However, these studies must be cautiously interpreted due to small sample sizes and the potential for selection bias. As there is no randomized or prospective data, there are no official guidelines regarding repeat hepatectomy. The European Association for the Study of the Liver suggests either resection or ablation for "a small subset" of patients with liver-only recurrence (128). It appears reasonable to resect recurrent iCCA if an R0 resection of all hepatic lesions can be achieved and there is no evidence of extrahepatic disease. Surgical candidates should be carefully selected for favorable tumor biology, and some centers advocate for re-resection only after a disease-free interval of over 3 months (127). Other criteria include good functional status and an appropriately sized liver remnant. Palliative resections should not be performed (129).

Using these criteria, only about 10-25% of patients with recurrence are eligible for resection (10, 126, 130, 131). In one of the larger multi-institutional studies, 400 patients developed intrahepatic-only recurrences, and 190 (47.5%) underwent some form of liver-directed therapy. Among this cohort, only 28.5% had a hepatic resection (10). In a multi-center Japanese study, the re-resection rate was 31% for patients with intrahepatic-only recurrences occurring after a year from the initial operation. For patients with earlier recurrences, repeat surgery was performed in only 6.8% (132). **Table 3** presents survival data after re-resection of iCCA liver recurrences. The heterogeneity of these data can be attributed to the site of recurrence, extent of resection, timing of surgery, and the use of systemic therapy.

Other studies have highlighted the drawbacks of liver-directed therapy, with more than half of patients in one multi-institutional study having a second recurrence within a year of repeat resection (10). Several studies have attempted to understand the factors that influence the benefit of a repeat resection. In one study, tumor biology (disease-free interval of ≤12 months) and extent of initial liver resection (major hepatectomy) decreased the likelihood that repeat liver resection would results in a long-term benefit (124). Margin status, CA 19-9 at time of primary resection, and time to recurrence have been identified as other important predictors of long-term outcome (133). In a large study of 72 patients who underwent R0 repeat resection for recurrent iCCA, recurrent tumor size larger than 3 cm, multiple recurrent nodules, cirrhosis, and time to recurrence of less than one year were all negatively associated with time from recurrence to death (129).

TABLE 3 | Survival after repeat resection for intrahepatic cholangiocarcinoma recurrence in the liver.

Authors	Years	Type	N	Median OS (months)	1-year OS	3-year OS	5-year OS
Bartsch et al. (133)	2008-2017	Multicenter	113	65.2	98%	78%	57%
Hyder et al. (134)	1990-2011	Multicenter	33	25.8 RTDS	–	–	–
Kamphues, et al. (135)	2002-2008	Single center	13	51*	–	–	–
Konstadoulakis et al. (136)	1991-2005	Single center	7	20 RTDS	–	–	–
Langella, et al. (124)	2002-2020	Single center	21	31	–	–	–
Murakami et al. (137)	–	–	5	26 RTDS	–	–	–
Saiura et al. (138)	1995-2008	Single center	4	–	–	75%	50%
Si et al. (129)	2005-2013	Single center	72	45.1	97%	67%	412%
Souche et al. (130)	1997-2012	Multicenter	10	25 RTDS	–	40%	–
Spolverato et al. (10)	1990-2013	Multicenter	41	26.1* RTDS	–	–	–
Sulpice et al. (126)	1997-2011	Single center	4	–	100%	100%	75%
Yoh et al. (139)	1993-2015	Single center	7	–	–	71%	–
Zhang et al. (140)	2007-2011	Single center	32	20.3 RTDS	84%	17%	–

OS, overall survival.

**Some patients also underwent ablation.*

To date, systemic chemotherapy has often been used and was often gemcitabine-based. Adjuvant therapy with capecitabine has generally become the standard of care after the BILCAP trial was published in 2019, and its impact on eligibility for and survival after repeat resection is not yet known (141).

Tumor Ablation

Ablation for recurrent iCCA can also provide good local control, provided that tumors are smaller than 5 cm and not located near large vessels or in a subcapsular location (142). In a retrospective Korean study, 20 patients with 29 recurrent lesions were identified (143). Tumors had to be 5 cm or smaller in diameter, with no more than three tumors, as well as no vascular invasion or extrahepatic metastasis. Ablation was performed percutaneously under either conscious sedation or local anesthesia. Technical success (complete ablation on imaging 1 month after the procedure) was achieved in 97% of tumors. Mean local tumor progression-free survival was 29.8 months and was significantly longer in patients with tumors under 1.5 cm. Overall survival at one year was 70% but decreased to 21% at 3 years. A small Chinese study used slightly different inclusion criteria: one lesion under 7 cm in diameter, up to three lesions under 3 cm each, tumors visible on ultrasound, no portal vein thrombosis, Child-Pugh grade A or B, platelet count above 50,000, and control of extrahepatic metastasis (144). Overall, 18 RFA treatments were performed in 12 patients with post-hepatectomy recurrence. Ablation effectiveness was 94.7%. However, during a median follow-up of 29.9 months after ablation, 5 patients needed repeat ablation due to recurrence. Median local recurrence-free survival was 21 months.

In some studies, using ablation to treat recurrent iCCA has yielded comparable survival to hepatic resection. In a retrospective Chinese study, 32 patients were treated with margin-negative repeat resection and 77 with RFA or MWA (140). The difference between indications for the two therapies were that there were no tumor size limitations for resection whereas tumors had to be under 5 cm for ablation. Median overall survival (20.3 vs. 21.3, p = 0.996) and disease-free survival (9.07 vs. 6.8 months, p = 0.692) were not significantly different between hepatic resection and thermal ablation. While two patients who underwent ablation developed liver abscesses, the overall rate of complications for thermal ablation was less than that of surgical resection (3.9% vs. 46.9%, p<0.001).

Another retrospective study from China included 121 patients, 56 of whom underwent ultrasound-guided percutaneous MWA and 65 who underwent surgical resection (145). Inclusion criteria were: first recurrence after curative hepatectomy, tumors smaller than 5 cm, fewer than 3 tumors, no vascular invasion or extrahepatic disease, Child Pugh A-B, and refusal of liver transplant. Patients with serious medical comorbidities were excluded. Patients received MWA instead of surgical resection if they had an insufficient liver remnant, refused general anesthesia or surgery, or were deemed too high risk for surgical intervention. Interestingly, 40-50% of patients underwent preventative TACE after initial surgery. Median overall survival was similar between the two groups (31.3 months for MWA and 29.4 months for surgery, p=0.405). The incidence of major complications was 13.8% in the surgery group and 5.3% in the MWA group (p<0.001).

In another study, 40 patients with three or fewer metastasis, maximum tumor diameter of 5 cm, and no extrahepatic disease with 64 recurrent lesions were treated with percutaneous RFA (146). Multivariable analysis showed that patients with tumors under 2 cm and recurrence more than one year from curative resection benefited most from therapy. Three patients (7.5%) had a major complication which included two liver abscesses and a biliary stricture. During a median follow-up of 26 months after RFA, 34 (85%) of the patients developed either a local or systemic recurrence. Eight went on to receive repeat RFA, 2 underwent TACE, 6 received systemic chemotherapy, 2 underwent surgery, 5 received chemotherapy and radiation, and 11 received supportive care.

While small and prone to selection bias, these studies did suggest that ablation is safe and can achieve similar survival outcomes to surgical resection in select patients with limited disease. **Table 4** presents a summary of survival outcomes following ablation.

Arterially Directed Embolic Therapy

Locoregional intra-arterial therapy is a good option for patients with intrahepatic recurrence who are unable to undergo repeat hepatectomy and may have larger lesions not amenable to ablation. It can also be safely repeated if necessary (147). One retrospective study compared TACE and percutaneous MWA among 275 patients with unresectable intrahepatic recurrence after resection for iCCA (148). Patients were propensity score-matched on tumor markers, tumor size, grade, and extent of resection in addition to other clinical factors. After matching, TACE was associated with better overall (HR=0.69, 95% CI=0.47-0.98) and relapse-free survival (HR=0.69, 95% CI=0.47-0.99). Interestingly, the prognostic factors for TACE and MWA were different. For TACE, tumor size > 5 cm, poor differentiation, and major resection predicted worse survival. For MWA, poor differentiation, infection with hepatitis B,

TABLE 4 | Survival after ablation for intrahepatic cholangiocarcinoma recurrence in the liver.

Authors	Years	Type	N	Median OS (months)	1-year OS	3-year OS	5-year OS
Chu et al. (146)	1999-2019	Single center	40	26.6	67.2%	36.2%	18.3%
Fu et al. (144)	2000-2011	Single center	12	30	87.5%	37.5%	–
Kim et al. (143)	1999-2009	Single center	20	27.4	70%	–	–
Zhang et al. (140)	2007-2011	Single center	77	21.3	69.8%	20.5%	–

OS, overall survival.

cholelithiasis, and lymph node metastasis were independently associated with survival.

Transarterial radioembolization with labelled ^{90}Y can be used for large lesions and for patients with portal vein thrombosis. Sulpice et al. described their single-center experience with ^{90}Y (126). The regimen required two stages of arteriography – one to map the hepatic artery, embolize its extrahepatic branches, and quantify hepatopulmonary shunts, and the second to treat the tumor with ^{90}Y. The authors noted that treatment with ^{90}Y was associated with improved survival after recurrence ($p = 0.048$). Another study by Mosconi et al. assessed response to ^{90}Y in a population of 23 patients with unresectable iCCA, 70% of whom had prior hepatic resections and 34% of whom had prior trans-arterial embolization or chemoembolization (149). After a median follow-up of 16 months, median survival was 17.9 months from date of the radioembolization procedure. Patients who were treatment-naïve did significantly better than patients for whom ^{90}Y was preceded by other treatments (52 months vs. 16 months, p=0.009). Of note, 17% of patients received chemotherapy after ^{90}Y due to disease progression. In addition, intra-arterial therapy may be useful for patients with multiple recurrences. One study reported that 52.8% of patients who had treatment for recurrent disease and had a second recurrence underwent intra-arterial therapy (10).

Stereotactic Body Radiation Therapy (SBRT)

There are currently limited data on the efficacy of SBRT for iCCA and even less evidence in the recurrent setting. Even in the treatment of primary tumors, SBRT is commonly used as a salvage treatment with 29-67% of patients receiving another treatment first (150). It is primarily used as a palliative therapy in patients who are not candidates for other treatments. Jung et al. analyzed outcomes of 30 patients with recurrent cholangiocarcinoma treated with SBRT (151). SBRT doses were 30-60 Gy given in 3-5 fractions. Median survival was 13 months, 1-year overall survival was 53%, and 2-year overall survival was 28%. There was a significant survival difference between patients who recurred within 1 year of surgery (8 months) and patients who recurred more than a year after surgery (17 months) (p=0.007). Time to recurrence was the only significant prognostic variable for overall survival on multivariable analysis. Patients treated with SBRT for recurrent tumors did not have a statistically significant difference in overall survival compared to patients treated for primary tumors, which the authors ascribe to the smaller tumor volume for recurrent tumors. The authors suggest that patients with small and indolent recurrent tumors would most benefit from SBRT as a salvage therapy.

Hypofractionated (proton or photon) external beam radiation therapy also delivers ablative doses. Smart et al. used 37.5-67.5 Gy delivered in 15 fractions in 66 patients with unresectable iCCA, 5 of whom had a prior surgical resection and presented with local recurrence (152). Inclusion criteria included maximum tumor diameter of 12 cm for solitary tumors, no greater than 3 tumors, no extrahepatic disease, and Child-Pugh scores of A and B. Two-year local control was 84%, and 2-year overall survival was 58%. Grade 3+ toxicity was 11%. Only one patient had isolated local failure, but 64% of patients had a disease recurrence. Eight patients were treated with re-irradiation at first recurrence.

Combination Therapy

Given anatomic and clinical limitations, combining the above therapies is common, especially resection and ablation. In a study that included 12 centers in the U.S., 47.5% of patients with recurrent iCCA underwent treatment. Among those patients, 75.8% received liver-directed therapy ± systemic chemotherapy. Liver-directed therapy included resection ± ablation (28.5%), only ablation (18.7%), and intra-arterial therapy (52.8%). Patients who underwent repeat resection ± ablation had a median survival of 26.1 months compared to 25.5 months for patients who underwent ablation only and 9.6 months for patients who underwent intra-arterial therapy (p=0.01) (10). Kamphues et al. observed a 51 month overall median survival for 13 patients treated with 12 repeat liver resections and 8 ablations (135).

Salvage Liver Transplantation (SLT)

While perihilar cholangiocarcinoma has become an accepted indication for liver transplantation, liver transplantation for iCCA historically has been associated with poor overall survival and recurrence rates as high as 54% (153). However, more recent studies have suggested that favorable outcomes may be achieved in highly selected patients with iCCA, in particular patients with "very early" iCCA measuring ≤ 2 cm who have decompensated cirrhosis and individuals with larger, unresectable iCCA who exhibit stable disease after 6 months of gemcitabine-based chemotherapy. In addition, there are currently several clinical trials currently enrolling patients that are evaluating the role of liver transplantation for patients with iCCA who are not candidates for liver resection, including the exploratory TESLA trial which will include patients with liver-only recurrent iCCA after prior liver resection (154). However, given that there are currently no published data regarding liver transplant for recurrent iCCA, SLT is not a standard treatment modality.

CONCLUSION

Among patients with resectable intrahepatic recurrence of CRCLM, HCC, or iCCA, repeat hepatectomy is generally the treatment of choice in selected patients as it has been associated with improved survival versus other treatment modalities. However, among patients with recurrent HCC who cannot tolerate a liver resection due to underlying cirrhosis, salvage liver transplantation provides comparable overall survival and possibly improved recurrence-free survival versus repeat hepatectomy. For patients with tumors ≤ 3 cm in diameter, ablative therapy with RFA or MWA may provide similar survival benefit to repeat hepatectomy and is preferred in patients who are not candidates for major surgery due to comorbidities. While not as efficacious as repeat resection or ablation, TACE, ^{90}Y,

and SBRT are other liver-directed therapies that can provide improved disease control and a modest survival benefit for patients with recurrent liver disease.

AUTHOR CONTRIBUTIONS

CA and ME contributed to the conception and design of the work, acquisition and interpretation of data for the work, drafting and revising of the work, providing approval of the work, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TP contributed to the conception and design of the work, drafting and revising of the work, providing approval of the work, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Transarterial Chemoembolization for Hepatocellular Carcinoma in Clinical Practice: Temporal Trends and Survival Outcomes of an Iterative Treatment

Filippo Pelizzaro[1], Selion Haxhi[1], Barbara Penzo[1], Alessandro Vitale[2], Edoardo G. Giannini[3], Vito Sansone[4], Gian Ludovico Rapaccini[5], Maria Di Marco[6], Eugenio Caturelli[7], Donatella Magalotti[8], Rodolfo Sacco[9], Ciro Celsa[10,11], Claudia Campani[12], Andrea Mega[13], Maria Guarino[14], Antonio Gasbarrini[15], Gianluca Svegliati-Baroni[16], Francesco Giuseppe Foschi[17], Andrea Olivani[18], Alberto Masotto[19], Gerardo Nardone[20], Giovanni Raimondo[21], Francesco Azzaroli[22], Gianpaolo Vidili[23], Maurizia Rossana Brunetto[24], Franco Trevisani[25] and Fabio Farinati[1] on behalf of Italian Liver Cancer (ITA.LI.CA) group*

[1] Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padova, Padova, Italy, [2] Department of Surgery, Oncology and Gastroenterology, Hepatobiliary Surgery and Liver Transplantation Unit, University of Padova, Padova, Italy, [3] Gastroenterology Unit, Department of Internal Medicine, University of Genova, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Policlinico San Martino, Genova, Italy, [4] Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [5] Gastroenterology Unit, Fondazione Policlinico Universitario A. Gemelli, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Roma, Italy, [6] Medicine Unit, Bolognini Hospital, Seriate, Italy, [7] Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy, [8] Internal Medicine Unit, Department of Medical and Surgical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [9] Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy, [10] Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), Gastroenterology & Hepatology Unit, University of Palermo, Palermo, Italy, [11] Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.), University of Palermo, Palermo, Italy, [12] Department of Experimental and Clinical Medicine, Internal Medicine and Hepatology Unit, University of Firenze, Firenze, Italy, [13] Gastroenterology Unit, Bolzano Regional Hospital, Bolzano, Italy, [14] Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Napoli "Federico II", Napoli, Italy, [15] Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Università Cattolica del Sacro Cuore, Roma, Italy, [16] Gastroenterology Unit, Polytechnic University of Marche, Ancona, Italy, [17] Department of Internal Medicine, Ospedale per gli Infermi di Faenza, AUSL Romagna, Faenza, Italy, [18] Infectious Diseases and Hepatology Unit, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy, [19] Gastroenterology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Italy, [20] Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Napoli "Federico II", Napoli, Italy, [21] Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina, Messina, Italy, [22] Gastroenterology Unit, Department of Surgical and Medical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [23] Department of Medical, Surgical and Experimental Sciences, Clinica Medica Unit, University of Sassari, Azienda Ospedaliero-Universitaria di Sassari, Sassari, Italy, [24] Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory and Internal Medicine Unit, University of Pisa, Pisa, Italy, [25] Medical Semeiotics Unit, Department of Medical and Surgical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Background: Transarterial chemoembolization (TACE) is one of the most frequently applied treatments for hepatocellular carcinoma (HCC) worldwide. In this study, we aimed at evaluating whether and how TACE application and repetition, as well as the related outcome, have changed over the last three decades in Italy.

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Mediterranean Institute for Transplantation and Highly Specialized Therapies (ISMETT), Italy
Jiasheng Cao,
Sir Run Run Shaw Hospital, China

***Correspondence:**
Fabio Farinati
fabio.farinati@unipd.it

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Methods: Data of 7,184 patients with HCC were retrieved from the Italian Liver Cancer (ITA.LI.CA) database. Patients were divided according to the period of diagnosis in six cohorts: P1 (1988–1993), P2 (1994–1998), P3 (1999–2004), P4 (2005–2009), P5 (2010–2014), and P6 (2015–2019). All the analyses were repeated in the overall patient population and in Barcelona Clinic Liver Cancer (BCLC) B patients, who are the subgroup of HCC patients originally supposed to receive TACE according to guidelines. TACE was defined as either the first or the main (more effective) treatment.

Results: The proportion of patients receiving TACE as first or main therapy declined over time, and less than 50% of BCLC B patients were treated with chemoembolization from P3 onward. Conversely, TACE was widely used even outside the intermediate stage. Survival of TACE-treated patients progressively increased from P1 to P6. Although TACE was performed only once in the majority of patients, there was an increasing proportion of those receiving 2 or ≥3 treatments sessions over time. The overall survival (OS) of patients undergoing repeated treatments was significantly higher compared to those managed with a single TACE (median OS 40.0 vs. 65.0 vs. 71.8 months in 1, 2, and ≥3 TACE groups, respectively; $p < 0.0001$). However, after a first-line TACE, the adoption of curative therapies provided longer survival than repeating TACE (83.0 vs. 42.0 months; $p < 0.0001$), which in turn was associated with better outcomes compared to systemic therapies or best supportive care (BSC).

Conclusions: Despite a decline in the percentage of treated patients over time, TACE has still an important role in the management of HCC patients. The survival of TACE-treated patients gradually improved over time, probably due to a better patient selection. Iterative TACE is effective, but an upward shift to curative therapies provides better outcomes while transition to systemic therapies and BSC leads to a worse prognosis.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, survival, iterative treatment, therapeutic hierarchy

INTRODUCTION

Liver cancer ranked as the sixth most common cancer and the third leading cause of cancer-related death worldwide in 2020, with approximately 906,000 incident cases and about 830,000 deaths (1). Hepatocellular carcinoma (HCC), which represents about 90% of primary liver cancers, is a leading cause of mortality among cirrhotic patients (2, 3). In most geographical areas, the annual HCC mortality almost equals its incidence, confirming the high mortality rate of this tumor [5-year survival rate of 12%–14% in the United States and 20% in Italy (4, 5)]. Despite efforts to foster surveillance programs, which could allow an earlier diagnosis and increase the percentage of patients amenable to curative treatments (6–8), HCC is frequently detected at an advanced stage, thus precluding the possibility to deliver curative treatments such as liver transplantation (LT), liver resection (LR), or ablation (ABL) (9).

According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, transarterial chemoembolization (TACE) is the standard-of-care treatment in patients with intermediate-stage HCC (9). However, it is also widely used outside the BCLC B stage and this makes TACE one of the most frequently used treatments for HCC in daily clinical practice worldwide (10, 11). TACE is by definition a palliative and iterative treatment, considering the low rates of complete response and the high risk of disease recurrence (12–14). There is no definitive evidence that scheduled TACE at regular intervals (e.g., every 2 months), irrespective of tumor response, has different effects on patient survival than on demand TACE. Nevertheless, the adoption of an aggressive schedule might lead to the development of liver failure in a high proportion of patients, most of whom are also affected by cirrhosis (15). Therefore, this approach has been substantially abandoned, following the recommendation of the guidelines to retreat with TACE only when residual viable tumor is detected at imaging, and to stop performing TACE when 2 subsequent attempts fail to obtain a significant oncologic response (9). Nevertheless, in clinical practice TACE is often repeated several times, particularly in patients with partial response or after recurrence following an initial successful treatment. However, the benefit of retreating with TACE is uncertain, also because survival prediction in these patients is a difficult issue that only complicated recalibration (16) or time-varying models (i.e., mHAP-III) (17) seem to accurately solve. This uncertainty has been increased by the growing availability of several lines of

effective systemic therapy based on tyrosine kinase inhibitors, ramucirumab and immunotherapy (18–23). Indeed, systemic therapy may be a valid (and possibly better) alternative to iterative TACE. In order to support the decision to retreat patients, several algorithms, such as ART score (24, 25) and ABCR score (26), have been proposed.

Although TACE is frequently used as treatment of HCC, few studies investigated whether its use has changed over time. Furthermore, little evidence is available regarding the percentage of patients retreated with TACE in real-life clinical practice, the changing trends of this percentage over time, and the outcome of patients retreated with transarterial therapies compared to other therapeutic options. Considering the availability in the Italian Liver Cancer (ITA.LI.CA) database of a large series of patients managed along a period of 30 years, our study aimed to evaluate whether in real-life clinical practice the use of TACE and its outcome have changed over time, as well as the oncologic and clinical characteristics that guide the choice of this treatment. Moreover, we evaluated temporal trends in the attitude to repeat TACE and outcomes of patients managed with iterative treatment sessions.

PATIENTS AND METHODS

Study Groups

In this retrospective study, data were retrieved from the ITA.LI.CA database, a multicenter registry including 7,817 HCC patients consecutively managed from January 1988 to December 2018 in 24 participating Institutions. Data are collected prospectively and updated every 2 years, and their accuracy is controlled by a data manager in the coordinating center (Bologna University).

The management of the ITA.LI.CA database conforms to the Italian legislation on privacy. According to Italian laws, specific patient consent is not mandatory for any retrospective analysis, but patients provided written informed consent for every diagnostic and therapeutic procedure, as well as for having their clinical data anonymously recorded in the database. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the ITA.LI.CA coordinator center (Bologna University; approval number 99/2012/O/Oss).

For the purpose of the present study, all patients with a diagnosis of HCC registered in the ITA.LI.CA database were considered eligible. The only exclusion criterion was the lack of data on variables relevant for the aim of this study, such as tumor stage and treatment. Therefore, from the entire population of patients included in the database (n = 7,817), 633 patients (8.1%) with missing data were excluded (in 153 patients, information on tumor burden or stage was missing, while treatment modality was not recorded in 480 cases), leaving 7,184 patients for the final analysis. These patients were divided in six 5-year cohorts on the basis of the year of diagnosis: P1 (1988–1993), P2 (1994–1998), P3 (1999–2004), P4 (2005–2009), P5 (2010–2014), and P6 (2015–2019). A flowchart of patient selection is provided in **Supplementary Figure 1**.

HCC diagnosis was histologically confirmed in 2,371 patients (33%), whereas in the remaining cases it was based on the radiological criteria (at computed tomography [CT] or magnetic resonance imaging [MRI]), according to guidelines available at the time of diagnosis (9, 27).

In the ITA.LI.CA database, demographic and clinicopathological data, such as age, sex, comorbidities, etiology of the underlying liver disease, main serological parameters [albumin, bilirubin, international normalized ratio (INR), creatinine, platelet count, alpha-fetoprotein (AFP)], Child–Pugh class, Model for End Stage Liver Disease (MELD) score, presence of ascites and hepatic encephalopathy, clinically relevant portal hypertension (CRPH), and Eastern Cooperative Oncology Group performance status (ECOG-PS), are recorded. CRPH diagnosis was based either on unequivocal signs (presence of splenomegaly, varices, ascites) or platelet count $<100 \times 10^9$/l (28). The database also reports main macroscopic tumor characteristics [location and size, number of nodules, macrovascular invasion (MVI), and extrahepatic spread (EHS)] evaluated with dynamic CT or MRI. In this study, also in order to evaluated the adherence to its therapeutic recommendation, for staging purposes we used the BCLC staging system (9).

The complete sequence of treatments for every patient is also registered in the ITA.LI.CA database. The following treatment groups were considered in the present study: liver transplantation (LT), liver resection (LR), ablative procedures (ABL: percutaneous ethanol injection, percutaneous or laparoscopic thermal ablation), TACE, trans-arterial embolization (TAE), selective internal radiation therapy (SIRT), systemic therapy with sorafenib or other tyrosine kinase inhibitors (SOR), best supportive care (BSC), and other treatments. In all the analyses, we evaluated the first therapeutic choice and the main (i.e., more effective) treatment according to the following hierarchy: LT, LR, ABL, TACE, TAE and SIRT, SOR, and BSC (29). The ITA.LI.CA database reports the treatment modality at each recurrence. In this study, when different rounds of TACE were necessary to achieve a complete treatment (e.g., treatment of lesions in the left lobe and subsequent treatment of nodules in the right lobe), TACE was considered as a single procedure. On the contrary, when repeated at tumor recurrence, TACEs were considered as separate treatments. Regarding technical details, in the ITA.LI.CA database, chemotherapeutic drugs administered as well as the type of TACE (conventional vs. drug-eluting beads) are rarely registered and were not considered in this study. Response to TACE was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and was categorized in complete response (CR), partial response (PR), stable disease (SD), and progressive disease (SD) (30).

Statistical Analysis

Categorical variables were reported as absolute and relative frequency (percentages), while quantitative variables as median and interquartile range (IQR). Mann–Whitney test was used to compare quantitative variables; meanwhile, χ^2 test and Fischer's exact test were used in the comparison of categorical variables as appropriate.

In order to evaluate predictors of TACE treatment compared to potentially radical (LT, LR, and ABL) and palliative (SOR and

BSC) treatments, a multinomial logistic regression was performed. Variables significantly or borderline ($p \leq 0.1$) associated with treatment category at univariate analysis were included in multivariate models. The multinomial logistic regression analysis was used to establish the variables predicting TACE as first and main treatment in the overall population of patients and in the subgroup of BCLC B patients.

Overall survival (OS), expressed as median and 95% confidence interval (CI), was calculated from diagnosis to death from any cause or last follow-up. For patients alive at the end of the study, survival was censored at December 31, 2018. Survival curves were calculated with the Kaplan–Meier method and compared with the log-rank test. The independent predictors of survival were identified by the multivariate Cox regression analysis, including in the analysis the variables associated with survival ($p \leq 0.1$) at the univariate analysis.

In all the analyses, a two-tailed p value <0.05 was considered as significant. Data were analyzed by IBM SPSS Statistics (version 25.0. Armonk, NY: IBM Corp) and GraphPad Prism version 8.3.1 (GraphPad Software, La Jolla, CA, USA).

RESULTS

TACE Treatment in the Whole Population

Baseline demographic and clinical characteristics of patients in the six time periods are described in **Table 1**. Compared to P1 patients, those diagnosed in more recent periods were slightly older, were more frequently diagnosed under surveillance, and had less frequently a viral etiology and cirrhosis. More than half of patients in all time periods had CRPH, with slightly lower percentages in P5 and P6. Liver function and AFP levels at diagnosis were similar among subgroups (except for a slightly lower MELD score in P5 and P6, and a lower median AFP level in P6). While the majority of patients presented with a single liver lesion at diagnosis in each time period, tumor size was significantly smaller in P2–P6 as compared to P1. As far as tumor stage at diagnosis is concerned, BCLC B patients progressively decreased, while the proportion of BCLC C patients increased over time.

The choice of prescribing TACE as the first therapeutic approach decreased across P2 and P3, remaining thereafter substantially stable. Namely, 45.7% of patients in P1, 45.9% in P2, 28.3% in P3, 28.9% in P4, 29.9% in P5, and 28.5% in P6 underwent TACE as first treatment (**Table 1** and **Figure 1A**). A very similar trend was demonstrated for TACE used as the main treatment (45.7%, 44.6%, 25.3%, 24.0%, 23.7%, and 22.9%, respectively) (**Table 1** and **Figure 1B**). In parallel to the decrease in TACE use, there was an increase of ABL and systemic therapies as both first and main treatments. The rate of LT and LR remained approximately stable across the six time periods considered.

TACE Treatment in BCLC B Patients

Of the entire population of patients included in the study, 1,270 (17.7%) were classified as BCLC B at the time of diagnosis. Baseline demographic and clinical characteristics of these patients in the six time periods considered are shown in **Table 2**. As in the whole population, patients diagnosed in recent time cohorts were slightly older and more frequently diagnosed with HCC under surveillance. Non-viral etiologies increased over time. No statistically significant differences in the percentage of patients with CRPH were demonstrated between different groups. A better residual liver function (as evaluated with Child–Pugh score and MELD) was documented in patients more recently diagnosed. As far as tumor burden is considered, the number of liver lesions was significantly lower in the more recent cohorts while the size of the largest nodule remained stable across the different calendar periods.

As in the whole population, even in BCLC B patients there was a decrease in the use of TACE as the first therapeutic approach between P2 and P3. In fact, 61.5% of patients in P1 and 65.3% in P2 were treated with chemoembolization, while these figures were 40.3% in P3, 47.7% in P4, 45.2% in P5, and 48.1% in P6 (**Table 2** and **Figure 1C**). Despite TACE being the standard of care according to BCLC guidelines, patients with intermediate-stage HCC diagnosed in more recent temporal cohorts underwent TACE as main treatment only in about one third of cases. Indeed, TACE was used as the main treatment in 61.5% of P1, 64.4% of P2, 37.5% of P3, 40.0% of P4, 37.2% of P5, and 39.0% of P6 patients (**Table 2** and **Figure 1D**). Notably, recently diagnosed BCLC B patients more frequently underwent to curative treatments (LR and ABL) as main therapies.

Beyond BCLC B patients, TACE was also widely used across all the other HCC stages (**Figure 2**). A substantial subgroup of BCLC 0 and A patients underwent TACE, as both first and main treatments, but even in these cases the use of such treatment dropped over time (from 36.0% in P1 to 9.6% in P6 as main treatment in BCLC 0; from 36.4% in P1 to 23.9% in P6 as main treatment in BCLC A). More than half of BCLC C patients were treated with TACE in P1 (52.9%), while this treatment was used in a lower proportion of patients both as first or main choice (25.1% and 21.2%, respectively) in P6.

Predictive Factors of Treatment With TACE

The multinomial logistic regression (**Table 3**) showed that, compared to potentially curative options (LT, LR, ABL), TACE was selected preferentially in older patients [adjusted odds ratio (aOR) = 0.88 per 10-year increase, 95% CI 0.82–0.94], in those with non-viral etiology (aOR = 0.82, 95% CI 0.69–0.97), with deteriorated clinical conditions (ECOG-PS ≥1), with CRPH (aOR = 0.51, 95% CI 0.43–0.60), and with poor residual liver function (aOR = 0.96, 95% CI 0.94–0.99, for MELD score). Moreover, patients with high tumor burden (number and size of liver lesions, and AFP levels) were less likely to receive LT/LR/ABL as the first therapeutic option. The same variables, with the addition of EHS (aOR = 0.54, 95% CI 0.36–0.83), were also negatively associated with LT/LR/ABL compared to TACE as main treatment. By contrast, patients with deteriorated clinical conditions (ECOG-PS ≥1), poor liver function, and high tumor burden (number and size of liver tumors, presence of MVI and

TABLE 1 | Baseline characteristics of the overall population of patients divided according to the period of diagnosis.

Variables	P1 (1988–1993) n=256	P2 (1994–1998) n=370	P3 (1999–2004) n=867	P4 (2005–2009) n=1323	P5 (2010–2014) n=2515	P6 (2015–2019) n=1853
Sex—males	197 (77.0)	279 (75.4)	657 (75.8)	1003 (75.8)	1932 (76.8)	1464 (79.0)
Age (years)	64 (58–68)	64 (57–70)	67 (61–74) [d]	68 (60–74) [d]	69 (60–75) [d]	69 (60–76) [d]
Surveillance	126 (49.2)	209 (56.5)	508 (58.6) [b]	831 (62.8) [d]	1637 (65.1) [d]	1073 (57.9) [a]
Etiology						
Viral	150 (58.6)	288 (77.8) [d]	613 (70.7) [c]	832 (62.9)	1443 (57.4)	941 (50.8) [a]
Not viral	54 (21.1)	45 (12.2) [b]	188 (21.7)	372 (28.1) [a]	815 (32.4) [c]	712 (38.4) [d]
Viral + other	52 (20.3)	37 (10.0) [c]	66 (7.6) [d]	119 (9.0) [d]	257 (10.2) [d]	200 (10.8) [d]
Liver disease						
Healthy liver	0 (0)	4 (1.1)	8 (0.9)	13 (1.0)	40 (1.6) [a]	41 (2.2) [b]
NAFLD	0 (0)	0 (0)	3 (0.3)	12 (0.9)	68 (2.7) [b]	50 (2.7) [b]
Fibrosis	6 (2.3)	7 (1.9)	49 (5.7) [a]	48 (3.6)	148 (5.9) [a]	139 (7.5) [b]
Cirrhosis	250 (97.7)	359 (97.0)	807 (93.1) [b]	1250 (94.5) [a]	2259 (89.8) [d]	1623 (87.6) [d]
ECOG-PS						
0	194 (75.8)	216 (58.4) [d]	698 (80.5)	923 (69.8)	1740 (69.2) [a]	1359 (73.3)
1–2	54 (21.1)	154 (41.6) [d]	166 (19.1) [d]	344 (26.0) [d]	672 (26.7) [d]	450 (24.3) [d]
3–4	8 (3.1)	0 (0) [c]	3 (0.3) [c]	56 (4.2)	103 (4.1)	44 (2.4)
CRPH	176 (68.7)	266 (71.9)	567 (65.4)	844 (63.8)	1514 (60.2) [b]	1128 (60.9) [a]
Child–Pugh						
A	170 (66.4)	234 (63.2)	552 (63.7)	889 (67.2)	1655 (65.8)	1305 (70.4)
B	75 (29.3)	105 (28.4)	256 (29.5)	340 (25.7)	757 (30.1)	465 (25.1)
C	11 (4.3)	31 (8.4)	59 (6.8)	94 (7.1)	103 (4.1)	83 (4.5)
MELD	10 (8–13)	10 (9–13)	10 (8–13)	10 (8–12)	10 (8–12) [b]	9 (8–11) [c]
AFP (ng/mL)	30.5 (9.0–201.5)	34.0 (9.0–172.8)	23.0 (7.0–210.0)	31.0 (6.0–330.0)	40.0 (5.0–567.0)	12.5 (4.0–239.3) [d]
Tumor morphology						
Monofocal	120 (46.9)	182 (49.2)	432 (49.8)	633 (47.8)	1267 (50.4)	990 (53.4)
Multifocal	112 (43.8)	169 (45.7)	375 (43.3)	587 (44.4)	1044 (41.5)	743 (40.1)
Infiltrative	15 (5.8)	15 (4.1)	33 (3.8)	69 (5.2)	141 (5.6)	61 (3.3) [a]
Massive	9 (3.5)	4 (1.1) [a]	27 (3.1)	34 (2.6)	63 (2.5)	59 (3.2)
Number	1 (1–4)	1 (1–4)	1 (1–3)	1 (1–3)	1 (1–2)	1 (1–2)
Diameter (cm)	3.5 (2.4–5.1)	3.0 (2.2–4.0) [a]	3.0 (2.2–4.5) [a]	3.0 (2.0–4.5) [b]	3.0 (2.0–5.0) [a]	3.0 (2.0–4.8) [c]
MVI	27 (10.5)	31 (8.4)	110 (12.7)	158 (11.9)	284 (11.3)	206 (11.1)
EHS	0 (0)	2 (0.5)	68 (7.8) [d]	139 (10.5) [d]	257 (10.2) [d]	189 (10.2) [d]
BCLC stage						
0	25 (9.8)	29 (7.8)	68 (7.8)	126 (9.5)	261 (10.4)	261 (14.1)
A	107 (41.8)	175 (47.3)	339 (39.1)	459 (34.7) [a]	934 (37.1)	685 (37.0)
B	78 (30.5)	101 (27.3)	216 (24.9)	235 (17.8) [d]	376 (15.0) [d]	264 (14.2) [d]
C	34 (13.3)	38 (10.3)	217 (25.0) [d]	439 (33.2) [d]	856 (34.0) [d]	594 (32.1) [d]
D	12 (4.7)	27 (7.3)	27 (3.1)	64 (4.8)	88 (3.5)	49 (2.6)
First treatment						
LT	5 (2.0)	16 (4.4)	28 (3.2)	34 (2.6)	49 (2.0)	33 (1.8)
LR	38 (14.8)	40 (10.8)	125 (14.4)	202 (15.3)	418 (16.6)	280 (15.1)
ABL	62 (24.3)	91 (24.6)	306 (35.3) [c]	430 (32.5) [b]	787 (31.3) [a]	608 (32.8) [b]
TACE	117 (45.7)	170 (45.9)	245 (28.3) [d]	383 (28.9) [d]	752 (29.9) [d]	528 (28.5) [d]
TAE/SIRT	0 (0)	0 (0)	1 (0.1)	3 (0.2)	21 (0.8)	75 (4.0) [d]
SOR	0 (0)	0 (0)	0 (0)	53 (4.0) [c]	229 (9.1) [d]	178 (9.6) [d]
BSC	6 (2.3)	7 (1.9)	78 (9.0) [c]	146 (11.0) [d]	218 (8.7) [d]	116 (6.3) [b]
Other	28 (10.9)	46 (12.4)	84 (9.7)	72 (5.5) [b]	41 (1.6) [d]	35 (1.9) [d]

(Continued)

TABLE 1 | Continued

Variables	P1 (1988–1993) n=256	P2 (1994–1998) n=370	P3 (1999–2004) n=867	P4 (2005–2009) n=1323	P5 (2010–2014) n=2515	P6 (2015–2019) n=1853
Main treatment						
LT	5 (2.0)	22 (6.0) [a]	43 (5.0) [a]	83 (6.2) [b]	121 (4.8) [a]	86 (4.6) [a]
LR	38 (14.8)	40 (10.8)	127 (14.7)	214 (16.2)	432 (17.2)	306 (16.5)
ABL	62 (24.2)	90 (24.3)	315 (36.3) [c]	436 (33.0) [a]	862 (34.3) [b]	637 (34.4) [b]
TACE	117 (45.7)	165 (44.6)	219 (25.3) [d]	317 (24.0) [d]	597 (23.7) [b]	424 (22.9) [d]
TAE/SIRT	0 (0)	0 (0)	1 (0.1)	2 (0.2)	18 (0.7)	72 (3.9) [b]
SOR	0 (0)	0 (0)	0 (0)	53 (4.0) [c]	226 (9.0) [d]	176 (9.5) [d]
BSC	6 (2.4)	7 (1.9)	78 (9.0) [c]	146 (11.0) [d]	218 (8.7) [d]	116 (6.3) [b]
Other	28 (10.9)	46 (12.4)	84 (9.7)	72 (5.4) [b]	41 (1.6) [d]	36 (1.9) [d]

Continuous variables are reported as median and interquartile range (IQR), while categorical variables as absolute and relative frequencies.
The first cohort (1988–1993) is taken as reference in the comparison with other time periods.
[a] $p < 0.05$ and ≥ 0.01.
[b] $p < 0.01$ and ≥ 0.001.
[c] $p < 0.001$ and ≥ 0.0001.
[d] $p < 0.0001$.
NAFLD, non-alcoholic fatty liver disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; CRPH, clinically relevant portal hypertension; MELD, Model for End-Stage Liver Disease; AFP, alpha-fetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread; BCLC, Barcelona Clinic Liver Cancer; LT, liver transplantation; LR, liver resection; ABL, ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization; SIRT, selective internal radiation therapy; SOR, systemic therapy; BSC, best supportive care.

EHS) were more likely to receive systemic or palliative treatment as compared to TACE, as both first and main therapy. Diagnosis under regular surveillance was significantly associated with higher odds to receive TACE rather than SOR or BSC.

The role of residual liver function in the choice of treatment requires further clarification. Compared to TACE, while poor residual liver function was negatively associated with LT, LR, and ABL considered together, this was not the case of patients treated specifically with transplantation. Indeed, higher MELD was a negative predictor of treatment with TACE when compared to LT: with the increase of the MELD score, the probability of being treated with TACE as first (aOR = 0.92, 95% CI 0.87–0.97; p = 0.003) and main treatment (aOR = 0.95, 95% CI 0.91–0.99; p = 0.03) decreased. Poor residual liver function favors LT compared to TACE, but at the same time it might contraindicate LR (particularly when large resections are needed). Therefore, considering the low number of patients managed with LT, it is not surprising that grouping together all curative treatments, the detrimental effect of poor residual liver function on the possibility to treat patients with LR prevailed, and we found that higher MELD was associated with greater probability to receive TACE.

In BCLC B patients, negative independent predictors of potentially curative therapies as first treatment compared to TACE were older age (aOR = 0.78 per 10-year increase, 95% CI 0.65–0.93), presence of CRPH (aOR = 0.44, 95% CI 0.30–0.66), and higher number of liver lesions (aOR = 0.87, 95% CI 0.76–0.99) (**Supplementary Table 1**). As far as the main treatment is concerned, in addition to these variables (age, residual liver function, number of liver nodules), also MELD score (aOR = 0.91, 95% CI 0.85–0.98), size of liver lesions (aOR = 0.91, 95% CI 0.83–0.99), and the period of diagnosis were associated with the probability to receive LT/LR/ABL rather than TACE. Compared to patients diagnosed in P1, those diagnosed from P3 to P6 were more likely to receive potentially curative treatments. Only MELD score (aOR = 1.10, 95% CI 1.01–1.20) and tumor size (aOR = 1.13, 95% CI 1.03–1.23) were independently associated with higher odds of receiving SOR or BSC as first treatment instead of TACE in BCLC B patients. In this subpopulation, tumor diameter was also the only predictive variable independently associated with increased probability of being treated with SOR or BSC as main treatment (aOR = 1.10, 95% CI 1.01–1.21).

Survival Analysis

In the whole patient population, the median follow-up was 27.0 months (95% CI 12–54.4), and the median survival was 40.0 months (95% CI 38.4–41.6). The median survival of patients gradually improved from 28.0 months (95% CI 23.2–32.8) in P1 to 40.0 months (95% CI 36.9–43.1) in P5 and it was not evaluable in P6 ($p < 0.0001$) (**Figure 3A**).

Similar trends were observed in patients treated with TACE as initial treatment (median OS 21.0 months [95% CI 16.2–25.8] in P1, 42.0 months [95% CI 37.7–46.3] in P5 and not estimable in P6; $p < 0.0001$) (**Figure 3B**). Median OS was generally lower in patients treated with TACE as main therapy, but the improvement of prognosis over time was confirmed in this

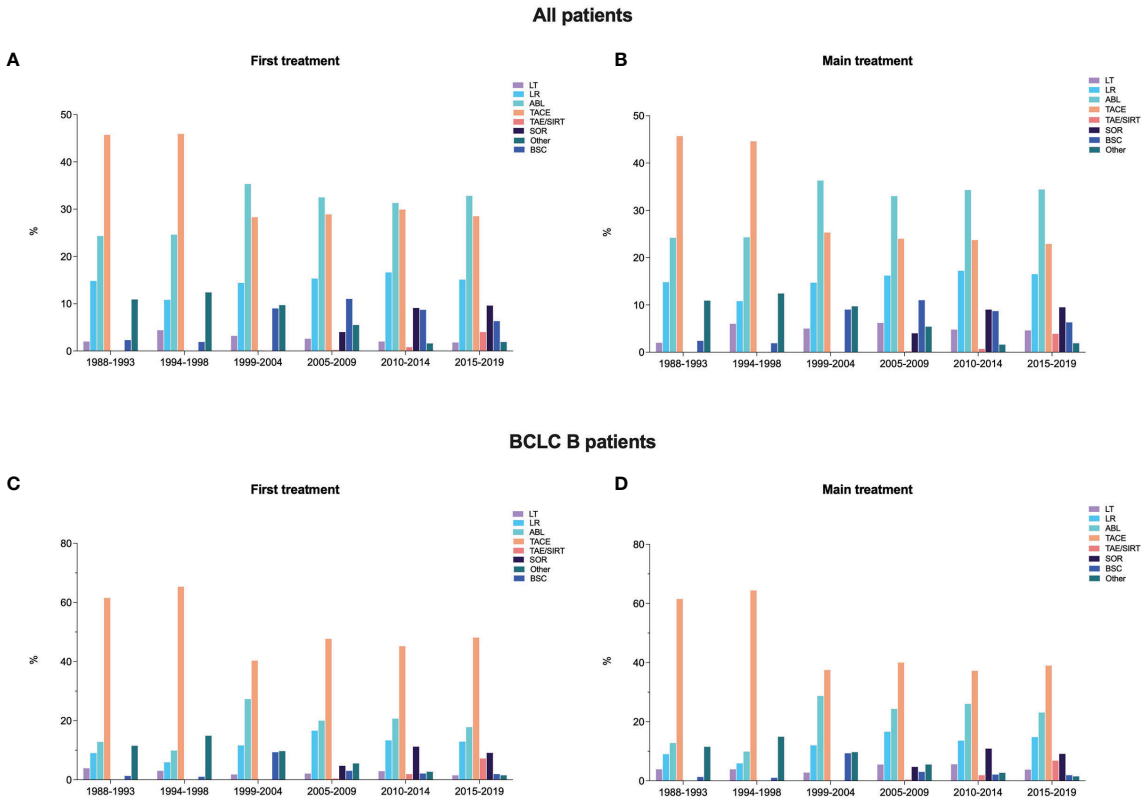


FIGURE 1 | Distribution of the first and main treatment adopted in the overall population of patients **(A, B)** and in BCLC B patients **(C, D)** in the six time periods considered.

subgroup (**Figure 3C**). After adjustment for confounders (age, etiology, surveillance, CRPH, MELD, AFP level, BCLC stage, and treatment, this latter only in the whole patient population), the improvement of survival over time was confirmed in all patients and in those treated with TACE as both first and main treatments (**Table 4**).

In BCLC B patients, the median follow-up was 24.0 months (95% CI 23.0–26.0) and the median OS was 32.0 months (95% CI 29.5–34.5). The median OS improved over time, from 16.0 months (95% CI 12.2–19.8) in P1 to 35.0 months (95% CI 30.0–40.0) in P5 and not estimable in P6 ($p < 0.0001$) (**Supplementary Figure 2A**). This gradual OS improvement was confirmed in intermediate-stage patients treated with TACE as both first (**Supplementary Figure 2B**) and main therapies (**Supplementary Figure 2C**). Similar to the results achieved in the whole patient population, the over time improvement of survival was confirmed after correction for confounders (**Supplementary Table 2**). Interestingly, in BCLC B patients a therapeutic hierarchy in terms of survival benefit (LT, LR, ABL, TACE, SOR, BSC) was demonstrated. Longer survival was shown in patients managed with potentially curative treatments compared to TACE which, in turn, was able to improve OS compared to systemic therapies (**Figure 4**). The independent prognostic role of treatment, with an established therapeutic hierarchy, was confirmed in BCLC B patients after adjustment for confounders (results of the Cox multivariate analysis are shown in **Supplementary Table 3**).

Temporal Trends and Survival of Patients Repeatedly Treated With TACE

Three thousand and seven patients (41.9%) underwent at least a TACE in their clinical history, irrespective of the treatment sequence adopted. The percentage of these patients remained substantially stable across the calendar periods considered, except for P6 in which a lower proportion of patients who received this treatment was registered (35.4%). In BCLC B patients, these percentages were higher compared to the overall population in all the time periods; P3 was the cohort with the lower number of TACE-treated patients (65.3%), while in P4 the highest proportion was registered (91.1%) (**Table 5**). Both in the whole patient population and in the BCLC B group, a forward shift of TACE treatment in the therapeutic sequence was observed over time. Indeed, the proportion of TACE applied as first-line treatment decreased, and consequently its adoption in second and subsequent lines increased (**Table 5** and **Supplementary Figure 3**). Treatment with TACE at recurrence (in second or subsequent lines), after the adoption of hierarchically superior treatments, was associated with better prognosis (**Figure 5**).

The objective response (CR+PR) to the first TACE was 79.8% in the whole population and 74.9% in BCLC B patients. No

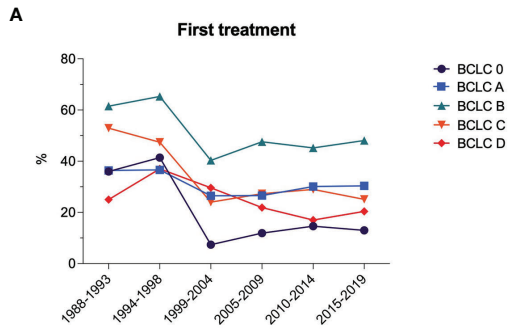
TABLE 2 | Baseline characteristics of the BCLC B patients divided according to the period of diagnosis.

Variables	P1 (1988–1993) n = 78	P2 (1994–1998) n = 101	P3 (1999–2004) n = 216	P4 (2005–2009) n = 235	P5 (2010–2014) n = 376	P6 (2015–2019) n = 264
Sex—males	68 (87.2)	76 (75.2)	164 (75.9) [a]	200 (85.1)	321 (85.4)	231 (87.5)
Age (years)	63 (58–68)	63 (57–70)	67 (60–73) [b]	66 (59–72) [b]	67 (59–74) [c]	68 (59–76) [c]
Surveillance	34 (43.6)	54 (53.5)	111 (51.4)	140 (59.6) [a]	221 (58.8) [a]	124 (47.0)
Etiology						
Viral	44 (56.5)	77 (76.2) [b]	151 (69.9) [a]	142 (60.4)	206 (54.8)	113 (42.8) [a]
Not viral	14 (17.9)	15 (14.9)	44 (20.4)	70 (29.8)	136 (36.2) [b]	111 (42.0) [d]
Viral + other	20 (25.6)	9 (8.9) [b]	21 (9.7) [b]	23 (9.8) [c]	34 (9.0) [c]	40 (15.2) [a]
Liver disease						
Healthy liver	0 (0)	3 (3.0)	1 (0.1)	1 (0.4)	13 (3.5)	3 (1.1)
NAFLD	0 (0)	0 (0)	2 (0.9)	3 (1.3)	9 (2.4)	11 (4.2)
Fibrosis	3 (3.8)	1 (1.0)	13 (6.0)	8 (3.4)	25 (6.6)	21 (8.0)
Cirrhosis	75 (96.2)	97 (96.0)	200 (92.6)	223 (94.9)	329 (87.5) [a]	229 (86.7) [a]
CRPH	51 (65.4)	72 (71.3)	130 (60.2)	131 (55.7)	202 (53.7)	158 (59.8)
Child–Pugh						
A	47 (60.3)	70 (69.3)	144 (66.7)	181 (77.0) [b]	283 (75.3) [a]	201 (76.1) [b]
B	31 (39.7)	31 (30.7)	72 (33.3)	54 (33.0)	93 (24.7)	63 (23.9)
MELD	11 (9-13)	11 (8–13)	10 (9–12)	10 (8–11) [a]	10 (8–11) [c]	9 (8–11) [c]
AFP (ng/mL)	40.0 (13.0-417.0)	30.5 (8.8–272.0)	50.0 (10.5–654.5)	39.5 (8.0–892.5)	92.0 (12.0–1158.0)	47.5 (7.0–1019.0)
Morphology						
2–3 lesions	2 (2.5)	4 (4.0)	35 (16.2) [b]	94 (40.0) [d]	224 (59.6) [d]	166 (62.9) [d]
>3 lesions	63 (80.8)	88 (87.1)	158 (73.1)	102 (43.4) [d]	111 (29.5) [d]	77 (29.2) [d]
Infiltrative/massive	13 (16.7)	9 (8.9)	23 (10.6)	39 (16.6)	41 (10.9)	21 (7.9) [a]
Number	4 (4-4)	4 (4–4)	4 (4–4) [a]	4 (2–4) [d]	3 (2–4) [d]	3 (2–4) [d]
Diameter (cm)	4.5 (3.5-6.7)	4.0 (2.9–5.0) [a]	4.0 (3.2–5.9)	4.0 (3.5–5.5)	4.0 (3.6–5.5)	4.0 (3.5–5.8)
First treatment						
LT	3 (3.9)	3 (3.0)	4 (1.8)	5 (2.1)	11 (2.9)	4 (1.5)
LR	7 (9.0)	6 (5.9)	25 (11.6)	39 (16.6)	50 (13.3)	34 (12.9)
ABL	10 (12.8)	10 (9.9)	59 (27.3) [a]	47 (20.0)	78 (20.7)	47 (17.8)
TACE	48 (61.5)	66 (65.3)	87 (40.3) [b]	112 (47.7) [a]	170 (45.2) [b]	127 (48.1) [a]
TAE/SIRT	0 (0)	0 (0)	0 (0)	1 (0.4)	7 (1.9)	19 (7.2) [b]
SOR	0 (0)	0 (0)	0 (0)	11 (4.7)	42 (11.2) [c]	24 (9.1) [b]
BSC	1 (1.3)	1 (1.0)	20 (9.3) [a]	7 (3.0)	8 (2.1)	5 (1.9)
Other	9 (11.5)	15 (14.9)	21 (9.7)	13 (5.5)	10 (2.7) [b]	4 (1.5) [c]
Main treatment						
LT	3 (3.9)	4 (3.9)	6 (2.8)	13 (5.5)	21 (5.6)	10 (3.8)
LR	7 (9.0)	6 (5.9)	26 (12.0)	39 (16.6)	51 (13.6)	39 (14.8)
ABL	10 (12.8)	10 (9.9)	62 (28.7) [b]	57 (24.3) [a]	98 (26.0) [a]	61 (23.1)
TACE	48 (61.5)	65 (64.4)	81 (37.5) [c]	94 (40.0) [b]	140 (37.2) [c]	103 (39.0) [c]
TAE/SIRT	0 (0)	0 (0)	0 (0)	1 (0.4)	7 (1.9)	18 (6.8) [a]
SOR	0 (0)	0 (0)	0 (0)	11 (4.7)	41 (10.9) [c]	24 (9.1) [b]
BSC	1 (1.3)	1 (1.0)	20 (9.3) [a]	7 (3.0)	8 (2.1)	5 (1.9)
Other	9 (11.5)	15 (14.9)	21 (9.7)	13 (5.5)	10 (2.7) [b]	4 (1.5) [c]

Continuous variables are reported as median and interquartile range (IQR), while categorical variables as absolute and relative frequencies.
The first cohort (1988–1993) is taken as reference in the comparison with other time periods.
[a] *$p < 0.05$ and ≥ 0.01.*
[b] *$p < 0.01$ and ≥ 0.001.*
[c] *$p < 0.001$ and ≥ 0.0001.*
[d] *$p < 0.0001$.*
NAFLD, non-alcoholic fatty liver disease; CRPH, clinically relevant porta hypertension; MELD, Model for End-Stage Liver Disease; AFP, alpha-fetoprotein; LT, liver transplantation; LR, liver resection; ABL, ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization; SIRT, selective internal radiation therapy; SOR, systemic therapy; BSC, best supportive care.

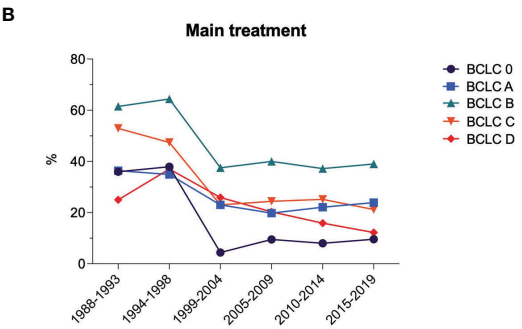
significant differences were demonstrated in radiological response, both overall and in BCLC B patients. In the whole population, patients with objective response had a longer median OS compared to non-responders [61.0 months (95% CI 56.0–66.0) vs. 41.0 months (95% CI 34.3–47.7); p < 0.0001) (**Supplementary Figure 4A**). A statistically significant difference in survival between responders [46.2 months (95% CI 40.9–51.5)] and non-responders [32.1 months (95% CI 21.2–43.0)] was also demonstrated in BCLC B patients (p = 0.004) (**Supplementary Figure 4B**).

While in P1–P3 periods the vast majority of patients received only one session of TACE (91.8%–100.0%), in P4–P6 periods a significantly higher percentage of patients received ≥2 TACEs. An increase over time of the percentage of patients treated with several TACE sessions was also observed in BCLC B patients (**Table 5**). Nevertheless, in all calendar periods, both overall and in the intermediate stage, the percentage of patients treated with only 1 TACE was above 50%. The median OS of patients receiving only one TACE [40.0 months (95% CI 37.7–42.3)] was significantly lower compared to patients receiving 2 [65.0



Percentage of patients treated with TACE:

BCLC 0	36.0	41.4	7.4	11.9	14.6	13.0
BCLC A	36.4	36.6	26.6	26.6	30.1	30.4
BCLC B	61.5	65.3	40.3	47.6	45.2	48.1
BCLC C	52.9	47.4	24.0	27.3	29.0	25.1
BCLC D	25.0	37.0	29.6	21.9	17.0	20.4



Percentage of patients treated with TACE:

BCLC 0	36.0	37.9	4.4	9.5	8.0	9.6
BCLC A	36.4	34.9	23.0	19.8	22.1	23.9
BCLC B	61.5	64.4	37.5	40.0	37.2	39.0
BCLC C	52.9	47.4	23.0	24.4	25.2	21.2
BCLC D	25.0	37.0	25.9	20.3	15.9	12.2

FIGURE 2 | Proportion of patients treated with TACE as first **(A)** and main **(B)** treatment in the six time periods considered, according to the BCLC stage.

months (95% CI 57.1–72.9)] and 3 or more TACE sessions [71.8 months (95% CI 61.1–82.4)] ($p < 0.0001$) (**Figure 6A**). In BCLC B patients, comparable results were obtained [30.4 months (95% CI 27.4–33.4) vs. 61.0 (95% CI 49.3–72.7) vs. 66.0 (95% CI 47.0–85.0), respectively; $p < 0.0001$) (**Figure 6B**). Among the patients who received at least one TACE, 1,805 (60.0%) were dead at the end of the follow-up, mainly because of tumor progression (66.2%) and less frequently from liver decompensation (20.1%) or other causes (13.7%). The proportion of deaths from liver decompensation in patients treated with two (20.4%) and three or more TACEs (18.4%) was similar to that of patients receiving only one course of TACE (20.3%). The majority of patients in the three groups died from tumor progression (67.3% in the 1 TACE group, 61.3% in the 2 TACE group, and 65.8% in the ≥3 TACE group).

In assessing whether TACE repetition can be considered as a positive or negative approach to the HCC treatment, the OS of patients who underwent an additional TACE in case of non-response or at the time of recurrence was compared to that of patients subsequently treated by curative treatments (LT, LR, or ABL), with an upward shift, or by systemic treatments and BSC, with a downward transition. The upward shift after a TACE was associated with a significantly better survival compared to TACE repetition [83.0 months (95% CI 64.3–101.8) vs. 42.0 months (95% CI 38.4–45.7); $p < 0.0001$]. This latter, in turn, provided a survival advantage compared to systemic therapies [27.0 months (95% CI 22.3–31.7); $p < 0.0001$] or BSC [29.0 months (95% CI 26.6–31.4); $p < 0.0001$] (**Figure 7A**). Similarly, in BCLC B patients, the upward shift after TACE led to a longer survival compared to a second TACE session [69.0 months (95% CI 29.7–108.3) vs. 35.0 months (95% CI 29.6–40.4); $p = 0.002$]. Instead, the prognosis was similar in patients repeating TACE and in those receiving systemic therapies [27.4 months (95% CI 22.3–32.5); $p = 0.44$], while patients allocated to BSC had a significantly poorer prognosis [24.0 months (95% CI 21.9–26.1]; $p = 0.001$) (**Figure 7B**].

DISCUSSION

With the single exception of LT, in most instances a single treatment, all therapies used in patients with HCC can be considered as iterative. In fact, the risk of tumor recurrence is high even after curative treatments (31), and both LR and ABL have been demonstrated to be safe and effective when repeated (32–37). Also, systemic therapy can be seen as iterative, since drugs for first-, second-, and even third-line therapy are now available (18–23). TACE, one of the most frequently used therapeutic strategies worldwide (10), could be considered by definition an iterative treatment, based on the low rates of complete response achievable and the high recurrence risk with this approach (12–14). Local tumor progression can generally benefit from repeated TACE sessions, but subsequent intra-arterial treatments have been indicated as responsible for an impairment of liver function (15). Although the evidence of TACE effectiveness for HCC treatment dates back of about 20 years (12, 38), there is a lack of studies exploring whether and how the application of TACE and its relative survival benefit changed over time in real-life clinical scenarios. Moreover, even less is known on TACE when considered as an iterative treatment, with few data available regarding the proportion of patients undergoing repetitive sessions. In order to give an answer to these questions, we analyzed the ITA.LI.CA database, one of the largest registries in Europe collecting data of HCC patients managed in many referral Italian centers over more than three decades.

The results of this study indicate that, although declining over time, the percentage of patients treated with TACE remained

TABLE 3 | Multinomial logistic regression showing independent factors associated with probability of receive TACE compared to potentially curative treatment (LT, LR, and ABL) and palliative therapies (SOR and BSC).

Variables		Curative treatment (LT, LR, and ABL)		Palliative treatment (SOR and BSC)		Curative treatment (LT, LR, and ABL)		Palliative treatment (SOR and BSC)	
		First treatment				Main treatment			
		aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Sex	Females	Ref	–	Ref	–	Ref	–	Ref	–
	Males	0.95 (0.79–1.13)	0.54	0.81 (0.61–1.09)	0.15	1.00 (0.83–1.21)	0.98	0.82 (0.61–1.11)	0.19
Age (per 10-year increase)		0.88 (0.82–0.94)	0.0001	1.08 (0.97–1.21)	0.16	0.81 (0.75–0.87)	<0.0001	1.04 (0.92–1.16)	0.55
Period of diagnosis	P1	Ref	–	Ref	–	Ref	–	Ref	–
	P2	0.11 (0.01–0.88)	0.04	0.57 (0.03–10.75)	0.71	0.20 (0.03–1.37)	0.10	0.62 (0.03–114)	0.75
	P3	0.68 (0.20–2.35)	0.54	2.73 (0.42–17.98)	0.30	0.80 (0.23–2.79)	0.73	2.89 (0.45–18.75)	0.27
	P4	0.61 (0.18–2.08)	0.43	1.96 (0.30–12.69)	0.48	0.81 (0.23–2.79)	0.74	2.21 (0.35–14.13)	0.40
	P5	0.51 (0.15–1.75)	0.29	1.41 (0.22–9.12)	0.72	0.74 (0.22–2.53)	0.63	1.61 (0.25–10.20)	0.62
	P6	0.49 (0.14–1.67)	0.26	1.16 (0.18–7.49)	0.88	0.66 (0.19–2.26)	0.51	1.27 (0.20–8.14)	0.80
Etiology	Viral	Ref	–	Ref	–	Ref	–	Ref	–
	Not viral	0.82 (0.69–0.97)	0.02	1.02 (0.78–1.33)	0.90	0.82 (0.69–0.98)	0.03	1.01 (0.77–1.33)	0.93
	Viral+other	0.90 (0.69–1.17)	0.42	1.31 (0.89–1.94)	0.18	0.87 (0.66–1.14)	0.30	1.31 (0.88–1.96)	0.19
Surveillance	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	1.08 (0.91-1.27)	0.38	0.62 (0.48-0.79)	0.0001	1.05 (0.88–1.25)	0.57	0.62 (0.48–0.80)	0.0002
ECOG-PS	0	Ref	–	Ref	–	Ref	–	Ref	–
	1–2	0.65 (0.54–0.78)	<0.0001	2.54 (1.99–3.24)	<0.0001	0.63 (0.53–0.76)	<0.0001	2.46 (1.92–3.16)	<0.0001
	3–4	0.39 (0.17–0.87)	0.02	11.85 (6.25–22.46)	<0.0001	0.35 (0.15–0.77)	0.01	10.71 (5.59–20.55)	<0.0001
CRPH	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	0.51 (0.43–0.60)	<0.0001	1.05 (0.80–1.37)	0.75	0.60 (0.51–0.71)	<0.0001	1.11 (0.84–1.46)	0.48
MELD		0.96 (0.94–0.99)	0.001	1.09 (1.06–1.12)	<0.0001	0.96 (0.94–0.98)	0.0002	1.08 (1.05–1.11)	<0.0001
Number		0.66 (0.61–0.70)	<0.0001	1.16 (1.10–1.22)	<0.0001	0.70 (0.65–0.74)	<0.0001	1.14 (1.08–1.21)	<0.0001
Diameter (cm)		0.89 (0.86–0.93)	<0.0001	1.15 (1.10–1.21)	<0.0001	0.88 (0.84–0.92)	<0.0001	1.14 (1.08–1.19)	<0.0001
MVI	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	0.80 (0.58–1.11)	0.18	1.75 (1.22–2.49)	0.002	0.73 (0.53–1.01)	0.06	1.61 (1.12–2.31)	0.01
EHS	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	0.71 (0.47–1.09)	0.12	4.01 (2.71–5.93)	<0.0001	0.54 (0.36–0.83)	0.004	3.55 (2.40–5.26)	<0.0001
AFP (ng/mL)	≤20	Ref	–	Ref	–	Ref	–	Ref	–
	20–200	0.79 (0.66–0.95)	0.01	0.87 (0.64–1.18)	0.38	0.81 (0.66–0.98)	0.03	0.86 (0.63–1.18)	0.36
	>200	0.61 (0.51–0.74)	<0.0001	1.18 (0.90–1.55)	0.23	0.59 (0.49–0.72)	<0.0001	1.15 (0.87–1.51)	0.34

TACE treatment is the reference category of the multinomial logistic regression. OR < 1 indicates that the variable is associated with higher probability of being treated with TACE rather than the comparison category (potentially curative treatments or palliative treatments). OR > 1 indicates that the variable is associated with higher probability to be treated with potentially curative treatments (or palliative treatments) rather than TACE.

In the multivariate models, BCLC stage was not included in favor of its constituent variables (number of liver tumors, size MVI, EHS, ECOG-PS, and residual liver function). MELD was selected as the variable expressing residual liver function.

LT, liver transplantation; LR, liver resection; ABL, ablation; SOR, systemic therapy; BSC, best supportive care; aOR, adjusted odds ratio; CI, confidence interval; ECOG-PS, Eastern Oncology Group performance status; CRPH, clinically relevant portal hypertension; MELD, Model for End-Stage Liver Disease; MVI, macrovascular invasion; EHS, extrahepatic spread; AFP, alpha-fetoprotein.

rather elevated in all the calendar periods considered. TACE was indeed selected as first-line therapeutic choice in 45.7% of patients diagnosed in P1, and the percentage of these cases decreased from P3 onward, until a figure of 28.5% in the last cohort (P6). The same trend was demonstrated when TACE was considered as the main (most radical) treatment applied, and less than a quarter of patients underwent TACE in P4–P6. Similar trends were detected in BCLC B patients, for whom TACE is

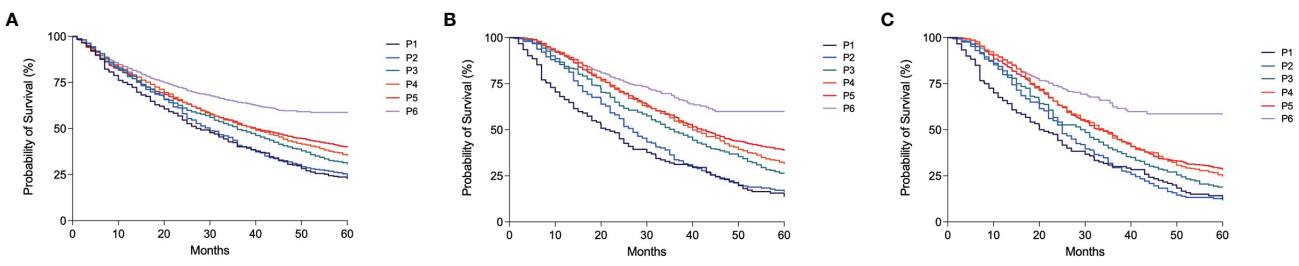


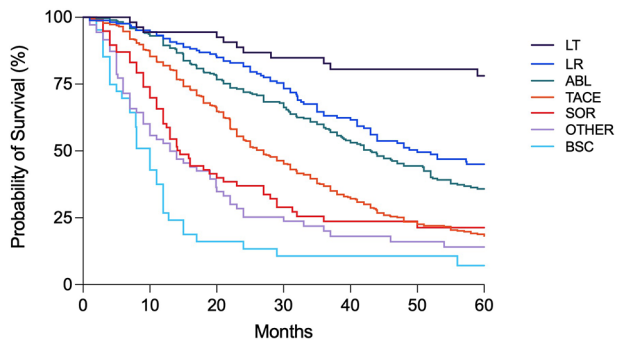
FIGURE 3 | Kaplan–Meier curves showing overall survival according to the period of diagnosis in the overall population of patients **(A)**, in patients treated with TACE as first treatment **(B)** and in those treated with TACE as main treatment **(C)** (all p < 0.0001).

TABLE 4 | Survival analysis according to the period of diagnosis in the overall population of patients.

Period of diagnosis	Median OS (months)	5-year survival (%)	aHR (95% CI)[a]	p
All patients				
P1	28.0 (23.2–32.8)	22.9	Ref	–
P2	28.0 (23.2–32.8)	24.2	1.00 (0.83–1.21)	0.99
P3	36.0 (32.6–39.4)	30.8	0.83 (0.71–0.98)	0.03
P4	39.9 (36.5–43.4)	35.4	0.67 (0.57–0.79)	<0.0001
P5	40.0 (36.9–43.1)	39.9	0.61 (0.52–0.71)	<0.0001
P6	NE (NE-NE)	58.5	0.49 (0.41–0.58)	<0.0001
Patients treated with TACE as first therapy				
P1	21.0 (16.2–25.8)	13.9	Ref	–
P2	27.0 (23.6–30.4)	16.6	0.96 (0.74–1.24)	0.74
P3	36.0 (31.4–40.6)	26.4	0.60 (0.46–0.77)	<0.0001
P4	40.0 (35.6–44.4)	31.6	0.51 (0.40–0.65)	<0.0001
P5	42.0 (37.7–46.3)	38.9	0.45 (0.36–0.57)	<0.0001
P6	NE (NE-NE)	59.7	0.31 (0.24–0.40)	<0.0001
Patients treated with TACE as main therapy				
P1	20.0 (15.0–25.0)	12.5	Ref	–
P2	25.0 (21.7–28.3)	11.9	0.97 (0.75–1.26)	0.84
P3	29.0 (23.8–34.1)	18.8	0.70 (0.54–0.90)	0.006
P4	34.0 (29.7–38.3)	24.8	0.61 (0.47–0.77)	<0.0001
P5	33.0 (29.3–36.6)	28.6	0.57 (0.45–0.73)	<0.0001
P6	NE (NE-NE)	58.6	0.38 (0.29–0.50)	<0.0001

[a]*Adjusted for: age, etiology, surveillance, CRPH, MELD, AFP level, BCLC stage, and main treatment (this latter only in the group including all patients).*
OS, overall survival; aHR, adjusted hazard ratio; NE, not estimable; TACE, transarterial chemoembolization.

considered as the standard-of-care treatment according to the BCLC algorithm (9). Although a decline in its application as both first and main therapy was shown, the proportion of patients treated with TACE has stabilized in the last temporal cohorts and it is unlikely to decline further, as it remains a well-established option in the therapeutic algorithm of patients with HCC.



Treatment	Median OS (months)	5-year survival (%)
LT	NE (NE-NE)	78.1
LR	50.0 (38.4-61.6)	45.0
ABL	43.0 (37.6-48.4)	35.7
TACE	27.0 (23.8-30.2)	18.2
SOR	14.5 (11.7-17.4)	16.0
OTHER	13.0 (7.2-18.8)	13.9
BSC	10.0 (7.6-12.4)	7.2

FIGURE 4 | Kaplan–Meier curves showing survival according to the main treatment modality in BCLC B patients ($p < 0.0001$). Median overall survival and 5-year survival rate are also shown for each treatment modality.

A not negligible proportion of patients in BCLC A, C, and D stages was treated with TACE, and also some very-early stage patients received this treatment. Similarly to the trend demonstrated in the overall patient population and in BCLC B, in the other stages the percentage of patients receiving TACE was higher in P1 and P2 and gradually decreased thereafter. These results show that, in our country, the real-life therapeutic management of HCC frequently deviates from the therapeutic recommendations of the BCLC algorithm. A study investigating the management of HCC in the Campania region of Italy (39), as well as numerous studies worldwide (10, 40–45), obtained comparable results regarding the poor adherence to guidelines, especially in intermediate and advanced stages. Indeed, adhering to BCLC therapeutic recommendations has been questioned by the vast amount of evidence demonstrating the better outcomes of patients undergoing treatments with potentially higher efficiency compared to the BCLC standard of care, and showing that the treatment is an independent predictor of survival within each BCLC stage (28, 42–48). Pertinently, a hierarchy of treatments in terms of survival benefit has been recently demonstrated in each tumor stage (29, 49). Treatment selection in patients with HCC is a difficult issue, and several variables have to be considered. They include not only tumor burden, residual liver function, and clinical conditions but also location of the tumor in the liver, presence of significant portal hypertension, comorbidities, patient preference, and, most importantly, the expected survival benefit of different treatment modalities. All of these are pivotal parameters that must be considered in order to tailor the treatment to the patient, with the aim of maximizing survival outcomes (49).

Despite being TACE the prototype of iterative treatments, our results demonstrated that in the "real life" of the ITA.LI.CA centers most patients (both overall and in BCLC B stage) are

TABLE 5 | Characteristics of TACE treatment in the different calendar periods.

	P1	P2	P3	P4	P5	P6
			All patients			
Patients with at least a TACE	123/256 (48.0)	195/370 (52.7)	354/867 (40.8)[a]	601/1323 (45.4)	1078/2515 (42.9)	656/1853 (35.4) [c]
Line of TACE treatment						
1st line	117 (95.1)	170 (87.2) [a]	245 (69.2) [d]	383 (63.7) [d]	752 (69.7) [d]	528 (80.5) [d]
2nd line	6 (4.9)	17 (8.7)	61 (17.2) [c]	143 (23.8) [d]	237 (22.0) [d]	102 (15.5) [c]
≥3rd line	0 (0)	8 (4.1) [a]	48 (13.6) [d]	75 (12.5) [d]	89 (8.3) [d]	26 (4.0) [a]
Rounds of TACE per patient						
1	123 (100.0)	194 (99.9)	325 (91.8) [c]	431 (71.7) [d]	631 (58.6) [d]	446 (68.0) [d]
2	0 (0)	0 (0)	9 (2.5)	102 (17.0) [d]	257 (23.8) [d]	141 (21.5) [d]
≥3	0 (0)	1 (0.1)	20 (5.7) [b]	68 (11.3) [d]	190 (17.6) [d]	69 (10.5) [d]
Response to first TACE						
CR + PR	96 (78.1)	164 (84.1)	274 (77.4)	475 (79.0)	863 (80.1)	529 (80.7)
SD + PD	27 (21.9)	31 (15.9)	80 (22.6)	126 (21.0)	215 (19.9)	127 (19.3)
TACE as main treatment	117/123 (95.1)	165/195 (84.6) [b]	219/354 (61.9) [d]	317/601 (52.7) [d]	597/1078 (55.4) [d]	424/656 (64.6) [d]
			BCLC B patients			
Patients with at least a TACE	61/78 (78.2)	82/101 (81.2)	141/216 (65.3) [a]	214/235 (91.1) [b]	329/376 (87.5) [a]	204/264 (77.3)
Line of TACE treatment						
1st line	48 (78.7)	66 (80.5)	87 (61.7) [a]	112 (52.3) [c]	170 (51.7) [d]	127 (62.3) [a]
2nd line	13 (21.3)	16 (19.5)	32 (22.7)	70 (32.7)	123 (37.4) [a]	56 (27.4)
≥3rd line	0	0	22 (15.6) [c]	32 (15.0) [c]	36 (10.9) [b]	21 (10.3) [b]
Rounds of TACE per patient						
1	61 (100.0)	82 (100.0)	134 (95.0)	156 (72.9) [d]	195 (59.3) [d]	131 (64.2) [d]
2	0 (0)	0 (0)	2 (1.4)	32 (15.0) [c]	75 (22.8) [d]	51 (25.0) [d]
≥3	0 (0)	0 (0)	5 (3.6)	26 (12.1) [b]	59 (17.9) [d]	22 (10.8) [b]
Response to first TACE						
CR + PR	45 (73.8)	65 (79.3)	108 (76.6)	163 (76.2)	234 (71.1)	157 (77.0)
SD + PD	16 (26.2)	17 (20.7)	33 (23.4)	51 (23.8)	95 (29.9)	47 (23.0)
TACE as main treatment	48/61 (70.7)	65/82 (79.3)	81/141 (57.4) [b]	94/214 (43.9) [d]	140/329 (42.6) [d]	103/204 (50.5) [c]

All patients receiving at least a TACE, irrespective of the treatment sequence adopted, were considered.
The first cohort (P1, 1988–1993) is taken as reference in the comparison with other time periods.
Continuous variables are reported as median and interquartile range (IQR), while categorical variables as absolute and relative frequencies.
[a] $p < 0.05$ and ≥ 0.01.
[b] $p < 0.01$ and ≥ 0.001.
[c] $p < 0.001$ and ≥ 0.0001.
[d] $p < 0.0001$.
TACE, trans-arterial chemoembolization; CR, complete response; OR, partial response; SD, stable disease; PD, progressive disease; BCLC, Barcelona Clinic Liver Cancer.

treated with TACE only once during their clinical history. In the most recent cohorts compared to the previous ones, a greater proportion of patients were treated with 2 or ≥3 sessions of TACE, but patients who repeated the treatment remained a minority. Considering the attitude to repeat the treatment according to response, presumably patients undergoing several sessions of TACE were those with good tumor responses and a delayed recurrence or a slow progression of the treated lesion(s). Indeed, the survival of patients managed with 2 and ≥3 TACE during their clinical history was significantly longer than that of patients treated with a single TACE course. Moreover, although immortal-time bias may have played a role, this result probably reflects also the better prognosis of those patients who can be retreated at recurrence thank to favorable oncologic and clinical

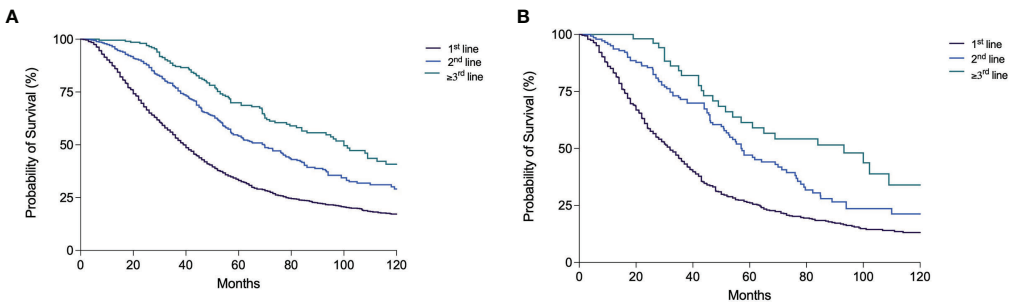


FIGURE 5 | Kaplan–Meier curves showing overall survival according to the line (1st, 2nd, ≥3rd) of TACE treatment during the patient clinical history in the overall patient population **(A)** and in BCLC B patients **(B)** (both $p < 0.0001$).

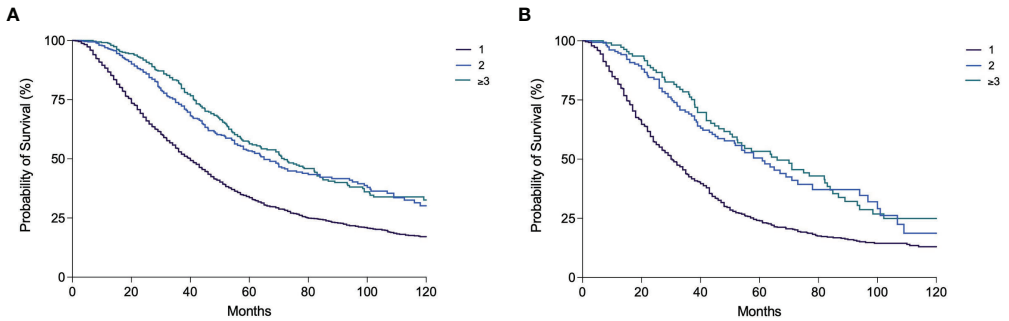


FIGURE 6 | Kaplan–Meier curves showing overall survival according to the number of TACE performed in the overall patient population **(A)** and in BCLC B patients **(B)** (both $p < 0.0001$).

characteristics. Interestingly, repeating TACE did not seem to be associated with an increased risk of death from liver decompensation, since the proportion of patients who died from liver failure was similar in those receiving 1, 2, or ≥3 treatment sessions. However, this comforting finding could not be reproduced if HCC patients are managed outside expert centers.

Although repeating TACE in clinical practice was effective and safe, we also demonstrated that, whenever possible, potentially curative treatments should be preferred to TACE repetition in case of non-response or at the time of cancer recurrence after the first transarterial treatment. In fact, regardless of the tumor stage as well as in BCLC B patients, the upward shift toward curative therapies (LT, LR, and ABL) made possible by TACE provided a longer survival compared to TACE repetition. The latter, in turn, was associated with better prognosis compared to systemic treatment or BSC. Since the survival of HCC patients is largely determined by the more effective treatment received, irrespective of the therapeutic sequence adopted (29), it was not surprising that, after a first-line TACE, the adoption of treatment that can provide a higher survival benefit was associated with better prognosis. Moreover, it has already been demonstrated that surgical treatment of HCC recurrence is a favorable prognostic factor (41, 50, 51). Therefore, the principle of firstly considering the therapy with the highest survival benefit is also valid in the second-line setting, in case of non-response or recurrence after the frontline therapy (49).

As expected, the variables impacting in treatment selection pertained to clinical conditions, residual liver function, and tumor burden. TACE was preferred to curative approaches in older patients, in those with ECOG-PS≥1, CRPH, higher MELD (except for LT specifically), and greater tumor burden (in terms of number and size of nodules, MVI, EHS, and high AFP levels). The opposite was found comparing TACE vs. more palliative treatments: patients who had compromised clinical conditions, higher MELD, increasing number and size of liver nodules, and presence of MVI or EHS were more likely to receive SOR or BSC. In BCLC B patients, age, CRPH, residual liver function, and number and size of liver nodules influenced the selection of treatment. However, the probability of being treated with potentially curative therapies instead of TACE as main treatment increased from P3 onward, suggesting that the attitude of treating intermediate-stage patients with curative intent, whenever feasible, has progressively gained field in recent years.

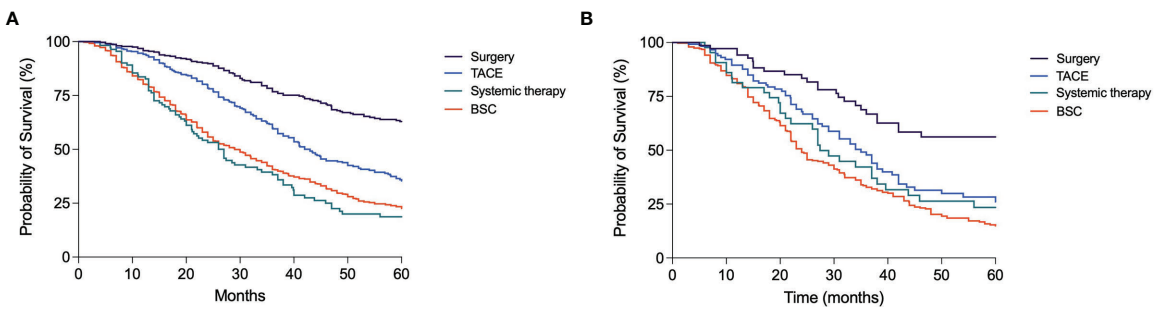


FIGURE 7 | Kaplan–Meier curves showing the survival of patients treated with TACE in first-line according to the subsequent treatment. **(A)** In the overall patient population, those allocated to surgery had a significantly longer OS compared to those receiving another TACE ($p < 0.0001$); these latter patients had in turn a better prognosis compared to those allocated to systemic therapies ($p < 0.0001$) or BSC ($p < 0.0001$). **(B)** In BCLC B patients, those treated with surgery had a better prognosis compared to patients repeating a second course of TACE ($p = 0.002$); these latter had a similar survival compared to patients treated with systemic therapies ($p = 0.44$) but maintained a significantly longer survival compared to those allocated to BSC ($p = 0.001$).

Another key finding of this study is the progressive improvement of survival over time, not only irrespective of treatment, but also in patients treated with TACE as first-line or main therapy. This improvement occurred also in BCLC B patients, even if the median OS registered were lower in this group. In general, the progressive prolongation of survival may be the result of an earlier HCC diagnosis, a better management and the availability of effective therapies for the underlying liver disease (52), and a better HCC management. In patients treated with TACE, a better selection of patients and technical advancements [e.g., superselective embolization to minimize ischemic injury to non-tumor tissue (53)] are probably the key determinants. In support to these considerations, it has already been demonstrated that refinements in the selection criteria, made possible by the publication of studies demonstrating TACE efficacy in selected patients, provided better survival outcomes despite the more advanced tumor stage of treated patients (54).

Despite this improvement, in intermediate-stage patients, TACE remained less effective in terms of survival benefit than curative treatments. As already reported (48), TACE provided worse outcomes compared to LT, LR, and ABL. Moreover, as the existence of a therapeutic hierarchy in BCLC B patients (LT > LR > ABL > TACE > SOR > BSC) was confirmed by our study, such evidence reinforces the concept that, whenever possible and once having excluded specific contraindications, the treatment potentially offering the best survival should be chosen irrespective of the stage (29, 49).

Despite its many strengths, our study also has some limitations, the most important of which is its retrospective nature which may have introduced unintended biases. Nevertheless, the aim of the study itself, which was to evaluate if and how the application of TACE and the attitude to repeat this treatment in clinical practice have changed in the last decades, required the analysis of a large dataset collecting real-life data. The ITA.LI.CA database offered us this opportunity, having collected data of HCC patients managed in clinical practice for more than three decades and being nowadays one of the largest European databases. However, the retrospective design of the study made it impossible to determine the exact reasons behind the choice of TACE as the first-line or main HCC treatment. Moreover, the reasons that prompted clinicians to prescribe additional TACE after a first session or to switch to other treatments were not predefined and standardized among centers. We tried to evaluate which factors were associated with a higher likelihood of receiving TACE compared to other treatments, but we could not consider all the variables implicated, including patients' unwillingness to accept the treatment, comorbidities, and technical contraindications. Another major limitation of this study is that we could not provide technical details about TACE treatment. This therapy, which can be grossly divided in conventional TACE (cTACE) and TACE with drug-eluting beads (DEB-TACE), lack in standardization and is a rather heterogeneous treatment (11). Unfortunately, in the ITA.LI.CA database a detailed description of the type of TACE is seldom available and therefore we could not assess the technical evolution of the procedure over time (which may partly explain the progressively better survival seen in recent years) and whether the attitude to treat patients with cTACE or DEB-TACE has changed. Technical skills and experience are fundamental for the effectiveness of TACE. Even though we did not measure these variables, all the Institutions collaborating to the ITA.LI.CA project are expert centers in the management of HCC patients that routinely performs TACE.

In conclusion, in this study we provided a comprehensive analysis of the changes in TACE treatment that have occurred in real-life clinical practice over the last three decades. The proportion of patients treated with TACE, also when BCLC B patients were specifically considered, declined over time but remained stable over the last calendar periods considered. In the real-world clinical management of HCC, a substantial proportion of BCLC B patients are managed deviating from treatment recommendations of Western guidelines, and a relevant percentage of patients belonging to other stages are treated with TACE, confirming that expert centers have a poor adherence to BCLC indications. The better selection of patients, as well as the procedural improvements, may explain the progressive better survival observed over time in patients undergoing TACE. Nevertheless, although this treatment could be safely and effectively repeated in expert centers, in this setting the majority of patients are treated with TACE only once during their clinical history. After a first-line TACE, a shift toward curative therapies (LT, LR, and ABL) to refine the achieved result provides a higher survival benefit compared to TACE repetition and, therefore, it should be preferred whenever feasible.

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 Independent Ethic Committee of S. Orsola-Malpighi hospital of Bologna. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

OTHER MEMBERS OF THE ITALIAN LIVER CANCER (ITA.LI.CA) GROUP

Department of Medical and Surgical Sciences, Semeiotics Unit, University of Bologna, Bologna: Maurizio Biselli, Paolo Caraceni, Lorenzo Lani, Annagiulia Gramenzi, Davide Rampoldi, Nicola Reggidori, Valentina Santi, Benedetta Stefanini.

Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna: Fabio Piscaglia, Francesco Tovoli, Alessandro Granito, Matteo Tonnini, Alma Di Carlo.

Department of Surgical and Medical Sciences, Gastroenterology Unit, Alma Mater Studiorum–University of Bologna, Bologna: Elton Dajti, Giovanni Marasco, Federico Ravaioli.

Department of Specialist, Diagnostic and Experimental Medicine, Radiology Unit, University of Bologna, Bologna: Alberta Cappelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli.

Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padova, Padova: Barbara Penzo, Elisa Pinto, Giorgio Palano, Federica Bertellini.

Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia: Ester Marina Cela, Antonio Facciorusso.

Gastroenterology Unit, Department of Internal Medicine, University of Genova, IRCCS Ospedale Policlinico San Martino, Genova, Italy: Giulia Pieri, Maria Corina Plaz Torres, Francesco Calabrese, Shirin Djahandideh.

Internal Medicine and Gastroenterology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma: Nicoletta de Matthaeis, Francesca Romana Ponziani.

Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona: Gloria Allegrini.

Gastroenterology Unit, Belcolle Hospital, Viterbo: Giorgia Ghittoni, Valentina Lauria, Giorgio Pelecca.

Medicina Protetta - Infectious Diseases Unit, Belcolle Hospital, Viterbo: Serena Dell'Isola.

Vascular and Interventional Radiology Unit, Belcolle Hospital, Viterbo: Fabrizio Chegai, Fabio Coratella, Mariano Ortenzi.

Infectious Diseases and Hepatology Unit, Azienda Ospedaliero-Universitaria of Parma, Parma: Gabriele Missale, Elisabetta Biasini.

Gastroenterology Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar: Alessandro Inno, Fabiana Marchetti.

Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties, PROMISE, Gastroenterology & Hepatology Unit, University of Palermo, Palermo: Giuseppe Cabibbo, Calogero Cammà, Paolo Giuffrida, Caterina Stornello, Mauro Grova, Carmelo Marco Giacchetto, Gabriele Rancatore, Maria Vittoria Grassini.

Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina, Messina: Maria Stella Franzè, Carlo Saitta.

Department of Medical, Surgical and Experimental Sciences, Azienda Ospedaliero-Universitaria of Sassari, Sassari: Assunta Sauchella.

Department of Internal Medicine, Ospedale per gli Infermi di Faenza, AUSL Romagna, Faenza: Vittoria Bevilacqua, Alberto Borghi, Marco Domenicali, Fabio Conti, Emanuela Giampalma, Lucia Napoli, Alessandro Mussetto.

Department of Experimental and Clinical Medicine, Internal Medicine and Hepatology Unit, University of Firenze, Firenze: Fabio Marra, Valentina Adotti, Martina Rosi, Stefano Gitto.

Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Napoli "Federico II", Napoli: Pietro Coccoli, Antonio Malerba.

Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Napoli "Federico II", Napoli: Filomena Morisco, Valentina Cossiga, Mario Capasso.

Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa, Pisa: Filippo Oliveri, Gabriele Ricco, Veronica Romagnoli.

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AUTHOR CONTRIBUTIONS

Conceptualization, FP, SH, BP, and FFa. Methodology, FP, FFa. Software, FT. Formal analysis, FP and FFa. Investigation, FP, SH, BP. Resources, FT. Data curation, BP, AV, EG, VS, GR, MDM, EC, DM, RS, CCe, CCa, AMe, MG, AG, GS-B, FFo, AO, AMa, GN, GR, FA, GV, MB, FT, FFa. Writing—original draft preparation, FP, SH, FFa. Writing—review and editing, BP, AV, EG, VS, GR, MDM, EC, DM, RS, CCe, CCa, AMe, MG, AG, GS-B., FFo, AO, AMa, GN, GR, FA, GV, MB, FT. Visualization, FFa. Supervision, FFa. Project administration, FP, FFa. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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A Novel Multimodal Radiomics Model for Predicting Prognosis of Resected Hepatocellular Carcinoma

Ying He[1†], Bin Hu[2†], Chengzhan Zhu[3], Wenjian Xu[2], Yaqiong Ge[4], Xiwei Hao[1], Bingzi Dong[5], Xin Chen[1], Qian Dong[1,5,6] and Xianjun Zhou[1,5*]*

[1] Department of Pediatric Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China, [2] Department of Radiology, The Affiliated Hospital of Qingdao University, Qingdao, China, [3] Department of Hepatobiliary and Pancreatic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China, [4] GE Healthcare, Shanghai, China, [5] Shandong Key Laboratory of Digital Medicine and Computer Assisted Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China, [6] Shandong College Collaborative Innovation Center of Digital Medicine Clinical Treatment and Nutrition Health, Qingdao University, Qingdao, China

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Alessandro Vitale,
University Hospital of Padua, Italy

Reviewed by:
Marco Massani,
ULSS2 Marca Trevigiana, Italy
Tingfan Wu,
GE Healthcare, China

***Correspondence:**
Xianjun Zhou
18661809968@163.com
Qian Dong
18661801885@163.com

[†]These authors have contributed equally to this work

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Objective: To explore a new model to predict the prognosis of liver cancer based on MRI and CT imaging data.

Methods: A retrospective study of 103 patients with histologically proven hepatocellular carcinoma (HCC) was conducted. Patients were randomly divided into training (n = 73) and validation (n = 30) groups. A total of 1,217 radiomics features were extracted from regions of interest on CT and MR images of each patient. Univariate Cox regression, Spearman's correlation analysis, Pearson's correlation analysis, and least absolute shrinkage and selection operator Cox analysis were used for feature selection in the training set, multivariate Cox proportional risk models were established to predict disease-free survival (DFS) and overall survival (OS), and the models were validated using validation cohort data. Multimodal radiomics scores, integrating CT and MRI data, were applied, together with clinical risk factors, to construct nomograms for individualized survival assessment, and calibration curves were used to evaluate model consistency. Harrell's concordance index (C-index) values were calculated to evaluate the prediction performance of the models.

Results: The radiomics score established using CT and MR data was an independent predictor of prognosis (DFS and OS) in patients with HCC ($p < 0.05$). Prediction models illustrated by nomograms for predicting prognosis in liver cancer were established. Integrated CT and MRI and clinical multimodal data had the best predictive performance in the training and validation cohorts for both DFS [(C-index (95% CI): 0.858 (0.811–0.905) and 0.704 (0.563–0.845), respectively)] and OS [C-index (95% CI): 0.893 (0.846–0.940) and 0.738 (0.575–0.901), respectively]. The calibration curve showed that the multimodal radiomics model provides greater clinical benefits.

Conclusion: Multimodal (MRI/CT) radiomics models can serve as effective visual tools for predicting prognosis in patients with liver cancer. This approach has great potential to improve treatment decisions when applied for preoperative prediction in patients with HCC.

Keywords: liver cancer, multimodal imaging, computed tomography, MRI, radiomics, nomogram

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver tumor, accounting for 75%–85% of liver cancers (1). HCC is the second most common cause of cancer death worldwide and has high morbidity and mortality rates (2). Surgical resection and local ablation remain the most commonly used radical treatment methods for HCC; however, tumors recur in 70% of cases after hepatectomy and 25% of cases after liver transplantation, and the 5-year overall survival (OS) rate is only approximately 25%–55% (3–5). Hence, patients with HCC have a poor prognosis after surgery, and the high disease recurrence rate represents a great challenge to successful treatment (3, 6). Therefore, the identification of reliable predictors of early recurrence is critical for patient risk stratification, support for treatment decisions, and improvement of long-term survival.

At present, relevant tumor factors, such as lesion diameter, cirrhosis, multifocality, poorly differentiated tumor, and microvascular invasion (MVI), are recognized as risk factors for early disease recurrence (7–10); however, most of these features can only be evaluated by postoperative histopathological examination, which is invasive, and the results are prone to a missed diagnosis. In oncology, the application of radiomics, which involves the transformation of traditional medical images into high-dimensional, quantitative, and exploitable imaging data, enables in-depth characterization of tumor phenotypes and has the potential to provide information on intra-tumor heterogeneity and predict posttreatment survival (11, 12). Multimodal machine learning is a method to process and interpret multimodal information through machine learning. Multimodal fusion is used to fuse multimodal information and perform targeted prediction classification or regression problems (13–15). Medical imaging can include data in different forms, such as CT, MRI, PET, ultrasound, and X-rays. In different guidelines, either CT or MRI is proposed as the best imaging modality for the diagnosis of HCC (16–18). Recent HCC management guidelines recognize an increasing role for gadoxetic acid-enhanced MRI in early diagnosis and monitoring post-resection (19). CT or MRI can all confirm the diagnosis if a nodule larger than 1-cm diameter is found with typical vascular features of HCC (hypervascularity in the arterial phase with washout in the portal venous or delayed phase) (20). Further, both CT and MR functional scans can be useful as supplements to conventional plain scan and dynamic enhancement to improve the accuracy of follow-up evaluation of liver cancer (21). In recent years, several qualitative MRI and CT imaging features have been reported. Preliminary evidence suggests that radiomics features have the potential to predict OS and tumor recurrence in patients with HCC, for example, by assessing peritumor parenchymal enhancement, satellite nodules, and non-smooth tumor margins, which are non-invasive predictors of early HCC recurrence (22–24).

Multimodal fusion technology can be divided into pixel level, feature level, and decision level, which are used to fuse abstract features and decision results in original data (13–15). To date, radiomics has been successfully applied in the study of nasopharyngeal carcinoma, non-small cell lung cancer, and rectal cancer (25–27), demonstrating the great potential for the development of this approach; however, to our knowledge, the use of contrast analysis of CT-enhanced sequence and MR-enhanced sequence data to assess patient prognosis remains rare. In this study, we combined these two novel imaging techniques and explored the performance of multimodal radiomics models derived from MR and CT image data for prognostic evaluation following HCC resection.

MATERIALS AND METHODS

Patients

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Due to its retrospective nature, the need for patient written informed consent was waived. From February 2014 to December 2020, we collected information from 306 patients with liver cancer, and 135 patients with primary HCC were recruited, based on the following inclusion criteria: 1) pathologically confirmed liver cancer recorded in the medical records at our hospital and 2) CT and MRI examinations performed within the previous 2 weeks before hepatectomy. The exclusion criteria were as follows: 1) other preoperative treatments [transarterial chemoembolization (TACE)], targeted drugs, and radiofrequency ablation), except hepatectomy (n = 11); 2) incomplete clinicopathological report (n = 10); 3) CT image and MR image quality was poor, and the

Abbreviations: HCC, hepatocellular carcinoma; DFS, disease-free survival; OS, overall survival; C-index, Harrell's concordance index; TACE, transarterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; ROI, region of interest; ICCs, the intra-class coefficient and the inter-class correlation coefficient; GLCM, gray-level co-occurrence features matrix-based features; GLRLM, gray-level run-length matrix-based features; GLSZM, gray-level size zone matrix-based features; GLDM, gray-level dependence matrix-based features; Log, Laplace wavelet; LASSO, least absolute shrinkage and selection operator; KM, Kaplan–Meier; Radscore, radiomics score; MVI, microvascular invasion; BMI, body mass index; PV_TT, portal vein tumor thrombosis; PLT, platelet count; HBsAg, hepatitis B surface antigen status; PT, prothrombin time; NEUT, neutrophil count.

lesion could not be recognized or the lesion image was less than three layers (n = 3); 4) lost to follow-up (n = 4); and 5) error occurred in the feature extraction process (n = 4). The final study population included 103 patients. The entire cohort was randomly divided into a training cohort (n = 73) and a validation cohort (n = 30) (ratio, 7:3). Training queues were used to build single-modal and multimodal radiomics models, which were evaluated using validation queues.

Clinical Endpoints and Follow-Up

The endpoints of this study were disease-free survival (DFS) and OS. DFS was measured from the date of surgery until disease progression, death from any cause, or the last visit in follow-up (censored), and nomograms were also built based on the DFS. Disease progression, including local recurrence distant metastasis, was confirmed by clinical examination and imaging methods such as abdominopelvic CT or MRI or was biopsy-proven. OS was defined as the time to death from any cause. All patients were followed up after surgery. Serum alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), albumin (ALB), and alpha-fetoprotein (AFP) levels were obtained. Liver ultrasound examination was performed monthly within the 3 months after surgery and once every 3 months thereafter. CT examination of the lungs and enhanced CT or MRI of the liver were performed every 3 months during the first 2 years and once every 6 months thereafter. The minimum follow-up period was 3 days after surgery, while the maximum follow-up time was 92.8 months.

Image Acquisition

CT Scanning Methods and Parameters

Three-stage enhanced scans of the upper abdomen were obtained using a German CT (SOMATOM Definition Flash, Siemens, Munich, Germany) and an American Discovery CT (GE Healthcare, Chicago, IL, USA). Scans ranged from the top of the liver to the lower edges of both kidneys. Scanning parameters were as follows: voltage, 120 kV; current, 200–350 mA; scanning layer thickness, 5 mm; layer spacing, 5 mm; and matrix, 512 × 512. For contrast-enhanced scanning, a double-barreled high-pressure syringe was used to inject iohexol, containing 350 mg/ml of iodine, *via* the peripheral vein (flow rate, 3.0 ml/s; dose, 1.5 ml/kg). The delay times for the arterial, venous, and equilibrium phases were 30, 60, and 120 s, respectively.

MRI Scanning Methods and Parameters

MRI scanning was conducted using a 3.0 T Signa HDXT MR superconducting apparatus and an 8-channel body-phase front coil. Rapid volume acquisition Liver Acquisition with Volume Acceleration (LAVA) imaging of the liver was conducted using the following parameters: repetition time (TR), 4.2 ms; echo time (TE), 2.0 ms; layer thickness, 4.8–5.4 mm; layer spacing, 1.4–2.7 mm; field, 42.0 × 33.6 cm; and matrix, 320 × 192. The contrast agent, gadolinium diethylenetriamine penta-acetic acid, was used for enhanced scanning (dose, 0.2 mmol/kg; injection flow rate, 2.0 ml/s). The delay times of the arterial, portal, and equilibrium phases were 20–23, 60, and 180 s, respectively.

Tumor Segmentation

The tumor region of interest (ROI) was manually delineated on multi-phase CT and MR images by a radiologist with more than 10 years of experience (Reader 1) using ITK-SNAP (version 3.6.0; http://www.itksnap.org) to segment each tumor CT stage and MR stage. A two-dimensional ROI of the largest section of the tumor was selected, outlined, and saved as an NII file. Two weeks later, Reader 1 randomly selected 50 HCC patients and delineated the ROI again to evaluate the intra-class correlation coefficient of ROI. Additionally, another radiologist (Reader 2) independently performed ROI mapping for the randomly selected 50 HCC patients to evaluate the inter-class correlation coefficient.

Image Preprocessing and Feature Extraction

At the beginning of extraction, pre-processing was necessary to improve discrimination between texture features. To eliminate the batch effect of different equipment, all the data were normalized through z-score standardization to a standard intensity range with a mean value of 0 and SD of 1, and the image slices were resampled to voxel size = 1 * 1 * 1 cm^3. With the use of IBSI compliant AK software (Analysis Kit Software, version 3.3.0, GE Healthcare), 1,217 radiomics features were extracted from CT and MR images, including first-order statistical features, morphological features, gray-level co-occurrence features, matrix-based features (GLCM), gray-level run-length matrix-based features (GLRLM), gray-level size zone matrix-based features (GLSZM), gray-level dependence matrix-based features (GLDM), and (Log) Laplace wavelet changes. Furthermore, intra-class and inter-class correlation coefficients (ICCs) were used to evaluate the intra-observer and inter-observer reproducibility of feature extraction. The intra-class correlation coefficient was calculated by comparing the ROI of Reader 1 twice. The inter-class correlation coefficient between the groups was evaluated by comparing the ROI of Reader 1 with that of Reader 2. When ICCs exceeded 0.75 both within and between observers, this feature was considered to have a good consistency. Finally, the ICC range for CT (Balance, Venous, and Artery) was 0.175–1, and 917 features with ICC > 0.75 were retained for each phase. The ICC range for MR (Balance, Venous, and Artery) was 0.256–1, and 946 features with ICC > 0.75 were retained.

Feature Selection and Model Construction

Features with ICC values > 0.75 both within and between groups were retained for further analysis. In the training set, features with $p < 0.05$ in univariate Cox regression analysis were retained, and Spearman's correlation analysis and Pearson's correlation analysis were applied to eliminate characteristics that were highly correlated (selected coefficient threshold $|r| = 0.8$). The least absolute shrinkage and selection operator (LASSO) Cox regression with 10-fold cross-validation was used for further feature screening. Then, features with non-zero coefficients selected by LASSO analysis were linearly weighted. Next, radiomics scores (Radscores) were calculated for each patient.

The Radscore was the result of the Cox regression radiomics model. It was the linear combination weighted by the corresponding LASSO coefficients of each feature selected of each patient, and patients were then divided into high-risk and low-risk groups, according to their best truncation value in each model and the labeled high-risk group (riskscore = 1) and the low-risk group (riskscore = 0). Kaplan–Meier (KM) analysis was used to plot DFS and OS curves, and the log-rank test was used to evaluate the differences between high-risk and low-risk groups. The same threshold was then applied to the validation queue. C-index values were used to evaluate the performance of the model.

Nomogram Construction

First, univariate Cox analysis was used to analyze risk factors and screen for features with $p < 0.05$. Clinical factors with $p < 0.05$ and Radscore for CT and MRI data combined (Combined_radscore) were included in the multivariate Cox stepwise regression model, to investigate independent predictors of survival in HCC patients. Clinical factors and Combined_radscore (with $p < 0.05$) in the univariate Cox analysis were enrolled to establish a nomogram to predict patients' 2-year, 4-year, and 5-year survival rates. C-index values were used to evaluate the performance of the model, and calibration curves were generated and discrimination ability was quantified to compare predicted and actual survival rates.

Statistical Analysis

All statistical analyses were performed using R3.5.1 (https://www.r-project.org/). A t-test or Mann–Whitney U test was used to evaluate differences in continuous variables, and the chi-square or Fisher's exact test to assess differences in categorical variables. Continuous numerical variables are represented by the median (25th percentile, 75th percentile), and categorical variables are represented by percentages. Shapiro's test function in the R package was used to test for normality. Spearman's correlation analysis and Pearson's correlation analysis were used to eliminate redundant features. Pearson's correlation analysis was used for the features that conform to the normal distribution, and Spearman's correlation analysis was used for the features that do not conform to normal distribution. The surv_cutpoint function in the R package was used to calculate optimal truncation values. The KM method and log-rank test were used to estimate DFS and OS. Calibration curves were used to evaluate the degree of alignment of nomograms. Two-sided p-values <0.05 were considered significant.

RESULTS

Patient Characteristics

Patient demographics and clinicopathological features are presented in **Table 1**. Of the 103 patients included in the study, 83 (80.6%) were male, and the median age of all patients was 57.0 (32.0–73.0) years. There were no statistically significant differences in clinicopathological factors between patients in the training (n = 73, 70%) and validation (n = 30, 30%) cohorts ($p = 0.558$–0.997). A total of 44 patients had death endpoints. The median values for DFS and OS of the total patient group (n = 103) were 25.9 (0.1–88.1) months and 43.7 (0.1–92.8) months, respectively.

Radiomics Signature Construction

Features retained after each feature dimension reduction are listed in **Supplementary Table S1**. Finally, for prediction of DFS, 7, 12, and 17 features were selected from CT, MRI, and their combined features, respectively, and used to build models. For prediction of OS, 8, 16, and 17 features were selected to establish the model from CT, MRI, and their combined features, respectively. The details of selected features of DFS and OS are included in **Supplementary Figure S1** and **Table S2**. The calculated CT_radscore, MRI_radscore, and Combined_radscore were based on selected features.

We performed the univariate Cox analysis to determine the role of clinical features of patients on DFS in HCC (**Table 2**). Three clinical characteristics, namely, tumor diameter, liver capsule invasion, and MVI were identified by univariate analysis ($p < 0.05$). Clinical features with $p < 0.05$ were included in backward stepwise multivariate regression analysis. The results show that MVI was an independent predictor of HCC in the multivariable analysis ($p < 0.05$). We performed the univariate Cox analysis to determine the role of clinical characteristics on the OS of patients in HCC (**Table 3**). Six clinical characteristics, namely, body mass index (BMI), tumor diameter, MVI, portal vein tumor thrombosis (PV_TT), platelet count (PLT), and Bleeding_volume were identified by univariate analysis ($p < 0.05$). Clinical characteristics with $p < 0.05$ were included in backward stepwise multivariate regression analysis. The results show that BMI, MVI, and Bleeding_volume were independent predictors of HCC in the multivariable analysis ($p < 0.05$). The clinical models were built based on clinical risk features, and the Clinical_score of each model was calculated.

Combined_radscore and clinical factors were included in univariate Cox regression for analyzing DFS, and factors with $p < 0.05$ were included in backward stepwise multivariate Cox regression analysis (**Table 4**). The results show that Radscore and MVI were independent predictors of HCC in the multivariable analysis ($p < 0.05$). Combined_radscore and clinical factors were included in univariate Cox regression for analyzing OS, and factors with $p < 0.05$ were included in backward stepwise multivariate Cox regression analysis (**Table 5**). The results show that Radscore, MVI, PLT, and Bleeding_volume were independent predictors of HCC in the multivariable analysis ($p < 0.05$). CT+MRI_Clinical Model was established based on significant clinical risk features and Radscore. CT+MRI+Clinical_score of the models were calculated.

CT_radscore, MRI_radscore, Combined_radscore, Clinical_score, and CT+MRI+Clinical_score were divided into a high-risk group and a low-risk group according to the optimal cutoff value of each group, and then DFS and OS KM curves were plotted. KM curves methods and log-rank test estimating DFS (**Figure 1**) in the training cohort showed that patients in the low-risk group had significantly better outcomes than those in the high-risk group (all log-rank $p < 0.05$) using the model. We then performed the same analyses in the validation cohort. Each model had similar results in the validation cohort ($p < 0.05$).

TABLE 1 | Demographic and clinicopathological characteristics of patients with liver cancer.

Variable		Training cohort (N = 73)	Validation cohort (N = 30)	*p*
Age (years),	>60	32 (0.44)	12 (0.40)	0.721
	≤60	41 (0.56)	18 (0.60)	
Gender	Male	60 (0.82)	7 (0.23)	0.520
	Female	13 (0.18)	23 (0.77)	
Alcohol abuse (%)	Present	13 (0.18)	6 (0.20)	0.794
	Absent	60 (0.82)	24 (0.80)	
AFP (ng/ml, %)	≤20	32 (0.44)	11 (0.37)	0.503
	>20	41 (0.56)	19 (0.63)	
HBV (%)	Present	63 (0.86)	23 (0.77)	0.231
	Absent	10 (0.14)	7 (0.23)	
HBsAg (%)	Positive	62 (0.85)	23 (0.77)	0.316
	Negative	11 (0.15)	7 (0.23)	
Pos_operation_TACE (%)	Present	29 (0.40)	10 (0.33)	0.543
	Absent	44 (0.60)	20 (0.67)	
Tumor diameter (cm, %)	≤5 cm	52 (0.71)	17 (0.57)	0.153
	>5 cm	21 (0.29)	13 (0.43)	
Tumor number (%)	≥2	8 (0.11)	3 (0.10)	0.835
	<2	65 (0.89)	27 (0.9)	
MVI (%)	Present	35 (0.48)	17 (0.57)	0.421
	Absent	38 (0.52)	13 (0.43)	
PV-TT (%)	Present	3 (0.04)	2 (0.07)	0.627
	Absent	70 (0.96)	28 (0.93)	
Satellite lesions (%)	Present	9 (0.12)	3 (0.10)	0.997
	Absent	64 (0.88)	27 (0.90)	
Liver cirrhosis (%)	Present	61 (0.84)	26 (0.87)	0.924
	Absent	12 (0.16)	4 (0.13)	
Surgical margin (%)	<1 cm	26 (0.36)	16 (0.53)	0.094
	≥1 cm	47 (0.64)	14 (0.47)	
Liver capsule invasion (%)	Present	39 (0.53)	13 (0.43)	0.352
	Absent	34 (0.47)	17 (0.57)	
Surgical approach (%)	Laparoscopy	22 (0.30)	10 (0.33)	0.750
	Non-laparoscopy	51 (0.70)	20 (0.67)	
Histopathological grading	I, II	41 (0.56)	16 (0.53)	0.793
	III, IV	32 (0.44)	14 (0.47)	
Child–Pugh score (%)	A	71 (0.97)	26 (0.87)	0.058
	B	2 (0.03)	4 (0.13)	
CNLC (%)	I, II	66 (0.90)	25 (0.83)	0.309
	III, IV	7 (0.10)	5 (0.17)	
Bleeding_volume (ml, %)	≤400	64 (0.88)	27 (0.90)	0.997
	>400	9 (0.12)	3 (0.10)	
BMI (kg/m^2)		25.28 (22.67, 26.57)	23.81 (21.87, 25.69)	0.209
ALT (IU/L)		38 (21, 69)	40.50 (26.50, 97.93)	0.408
AST (IU/L)		29 (21, 57)	31.5 (22.25, 64, 35)	0.452
TBIL (μmol/L)		17.07 (13.56–22.50)	18.31 (13.61, 25.65)	0.338
ALB (g/L)		40.05 (37.29, 43.41)	40.71 (37.25, 43.96)	0.836
PT (s)		10.5 (9.80, 11.10)	10.60 (9.83, 11.17)	0.825
PLT (10^9/L)		160 (127, 209)	164 (116, 190)	0.554
NEUT (10^9/L)		2.97 (2.12, 4.74)	3.51 (2.88, 4.52)	0.200
Lymphocyte (10^9/L)		1.9 (1.36, 3.77)	1.71 (1.43, 2.57)	0.862

BMI, body mass index; AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen status; MVI, microvascular invasion; PV-TT, portal vein tumor thrombosis; CNLC, China Liver Cancer Staging; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet count; NEUT, neutrophil count.

KM curves methods and log-rank test estimating OS (**Figure 2**) in the training cohort showed that patients in the low-risk group had significantly better outcomes than those in the high-risk group ($p < 0.05$). We then performed the same analyses in the validation cohort, and similar results were observed.

Development and Assessment of a Radiomics Nomogram

To provide the clinician with a quantitative method to predict patients' probability of 2-year, 4-year, and 5-year DFS and OS and to demonstrate the incremental value of the radiomics signature for individualized assessment of DFS and OS, both radiomics nomograms were built in the training cohort (**Figures 3A, B**).

For prediction of DFS, Radscore, tumor diameter, liver capsule invasion, and MVI were finally retained to establish a nomogram for DFS prediction (**Figure 3A**), and BMI, tumor diameter, PV_TT, PLT, Bleeding_volume, and Radscore were retained for use in establishing the prognostic prediction nomogram for OS (**Figure 3B**). The performance of each

TABLE 2 | Univariate and multivariate analyses of training cohort to identify patient clinical features with prognostic value for DFS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	0.994 (0.961–1.028)	0.708		
Gender	1.712 (0.723–4.055)	0.222		
BMI	1.014 (0.992–1.036)	0.229		
Alcohol	1.088 (0.506–2.342)	0.829		
Liver cirrhosis	1.436 (0.607–3.399)	0.410		
Histopathological grade	1.361 (0.842–2.199)	0.209		
Tumor diameter	1.128 (1.02–1.247)	<0.05	1.07 (0.96–1.19)	0.244
Liver capsule invasion	1.907 (1.036–3.509)	<0.05	1.41 (0.74–2.72)	0.299
Surgical margin	1.025 (0.963–1.091)	0.445		
Tumor number	1.329 (0.583–3.027)	0.499		
Satellite lesions	1.43 (0.602–3.393)	0.418		
MVI	4.338 (2.31–8.147)	<0.05	3.95 (2.07–7.54)	<0.05
PV_TT	1.412 (0.34–5.867)	0.635		
HBV	0.833 (0.352–1.971)	0.677		
HBsAg	0.999 (0.997–1.003)	0.953		
Surgical approach	1.198 (0.626–2.291)	0.585		
Pos_operation_TACE	1.652 (0.911–2.996)	0.099		
AFP	1.000 (0.999–1.000)	0.547		
PLT	0.999 (0.995–1.004)	0.806		
PT	1.002 (0.989–1.015)	0.749		
Alb	1.014 (0.949–1.084)	0.675		
TBIL	0.954 (0.907–1.003)	0.067		
ALT	1.001 (0.998–1.003)	0.594		
AST	1.001 (0.999–1.003)	0.307		
NEUT	1.088 (0.978–1.209)	0.120		
Lymphocyte	0.987 (0.96–1.016)	0.379		
Bleeding_volume	1.000 (0.999–1.000)	0.201		
Child–Pugh score	0.746 (0.103–5.422)	0.772		
CNLC	0.77 (0.464–1.278)	0.312		

BMI, body mass index; MVI, microvascular invasion; PV-TT, portal vein tumor thrombosis; HBsAg, hepatitis B surface antigen status; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; PLT, platelet count; PT, prothrombin time; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NEUT, neutrophil count; CNLC, China Liver Cancer Staging; HR, hazard ratio.

modal for predicting DFS and OS was evaluated by calculating C-index values (**Table 6**). In DFS analysis, the CT+MRI+Clinical model showed the best performance in the training cohort (C-index = 0.858; 95% CI, 0.811–0.905), followed by the CT+MRI model (C-index = 0.826; 95% CI, 0.767–0.885). The clinical model had the lowest predictive performance of C-index = 0.717 (95% CI, 0.648–0.786). In the validation cohort, the CT+MRI+Clinical model showed the best performance (C-index = 0.704; 95% CI, 0.563–0.845), followed by the clinical model (C-index = 0.657; 95% CI, 0.504–0.809). The MRI model had the lowest predictive performance of C-index = 0.587 (95% CI, 0.412–0.763).

For analysis of OS, CT+MRI+Clinical had the best predictive performance (C-index = 0.893; 95% CI, 0.846–0.940) in the training cohort, followed by the CT+MRI model (C-index = 0.865; 95% CI, 0.810–0.920); the CT model had the lowest predictive performance (C-index = 0.740; 95% CI, 0.650–0.830).

In the validation cohort, CT+MRI+Clinical had the best predictive performance (C-index = 0.738; 95% CI, 0.575–0.901), followed by the clinical model (C-index = 0.705; 95% CI, 0.597–0.803). The MRI model had the lowest predictive performance of C-index = 0.601 (95% CI, 0.401–801). The calibration curve showed the high accuracy of the nomograms for predicting DFS and OS both in the training dataset (**Figures 3C, D**).

DISCUSSION

Previous studies have developed multimodal imaging models, using radiomics features determined by MR and CT to predict tumor prognosis (28). To our knowledge, the present study is the first to evaluate DFS and OS in patients with HCC using a contrastive learning analysis of enhanced CT and MRI sequence data. The main challenges faced by multi-pattern methods are how to judge the confidence of each mode and the correlation between modes, how to reduce the dimension of multi-pattern characteristic information, and how to register multi-pattern data collected asynchronously (13–15). We compared the advantages of multimodal radiomics models for CT and MRI integration.

Radiomics has recently received attention in the field of cancer research because it is a high-throughput method used to extract large numbers of radiomics features from standard medical imaging and can improve medical decisions (29). Radiomics is used to extract quantitative feature data that

TABLE 3 | Univariate and multivariate analyses of training cohort to identify patient clinical features with prognostic value for OS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	1.018 (0.98–1.057)	0.351		
Gender	0.484 (0.215–1.092)	0.081		
BMI	0.881 (0.798–0.972)	<0.05	0.850 (0.740–0.970)	<0.05
Alcohol	0.92 (0.378–2.240)	0.853		
Liver cirrhosis	0.952 (0.383–2.367)	0.916		
Histopathological grade	1.695 (0.965–2.977)	0.066		
Tumor diameter	1.188 (1.063–1.327)	<0.05	1.100 (0.910–1.320)	0.329
Liver capsule invasion	1.853 (0.888–3.867)	0.100		
Surgical margin	1.053 (0.991–1.120)	0.096		
Tumor number	0.947 (0.419–2.139)	0.895		
Satellite lesions	1.136 (0.339–3.805)	0.836		
MVI	6.935 (2.962–16.239)	<0.05	5.060 (2.080–12.310)	<0.05
PV_TT	3.87 (1.142–13.114)	<0.05	3.190 (0.870–11.650)	0.079
HBV	0.555 (0.212–1.454)	0.231		
HBsAg	0.998 (0.994–1.001)	0.155		
Surgical approach	1.267 (0.599–2.680)	0.535		
Pos_operation_TACE	1.305 (0.641–2.658)	0.463		
AFP	1.000 (0.999–1.000)	0.136		
PLT	0.993 (0.986–1.000)	<0.05	0.990 (0.990–1.000)	0.174
PT	1.003 (0.982–1.024)	0.812		
Alb	1.003 (0.932–1.080)	0.937		
TBIL	0.989 (0.952–1.028)	0.579		
ALT	0.999 (0.995–1.002)	0.500		
AST	0.998 (0.994–1.003)	0.478		
NEUT	1.07 (0.900–1.273)	0.442		
Lymphocyte	0.975 (0.936–1.015)	0.219		
Bleeding_volume	1.001 (1.001–1.002)	<0.05	1.000 (1.000–1.010)	<0.05
Child–Pugh score	1.784 (0.237–13.428)	0.574		
CNLC	1.313 (0.787–2.190)	0.298		

BMI, body mass index; MVI, microvascular invasion; PV-TT, portal vein tumor thrombosis; HBsAg, hepatitis B surface antigen status; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; PLT, platelet count; PT, prothrombin time; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NEUT, neutrophil count; CNLC, China Liver Cancer Staging; HR, hazard ratio.

TABLE 4 | Univariate and multivariate analyses of training cohort to identify patient clinical features and Combined_radscore with prognostic value for DFS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Tumor diameter	1.128 (1.020–1.247)	<0.05	1.290 (0.660–2.520)	0.456
Liver capsule invasion	1.907 (1.036–3.509)	<0.05	0.970 (0.870–1.080)	0.593
MVI	4.338 (2.310–8.147)	<0.05	3.090 (1.520–6.310)	<0.05
Radscore	6.553 (3.975–10.803)	<0.05	5.600 (3.340–9.370)	<0.05

DFS, disease-free survival; MVI, microvascular invasion; Radscore, radiomics score; HR, hazard ratio.

TABLE 5 | Univariate and multivariate analyses of training cohort to identify patient clinical features and Combined_radscore with prognostic value for OS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
BMI	0.881 (0.798–0.972)	<0.05	0.970 (0.880–1.060)	0.480
Tumor diameter	1.188 (1.063–1.327)	<0.05	0.840 (0.660–1.080)	0.174
MVI	6.935 (2.962–16.239)	<0.05	4.110 (1.550–10.87)	<0.05
PV_TT	3.870 (1.142–13.114)	<0.05	2.030 (0.510–8.160)	0.318
PLT	0.993 (0.986–1.000)	<0.05	0.990 (0.980–1.000)	<0.05
Bleeding_volume	1.001 (1.001–1.002)	<0.05	1.000 (1.000–1.010)	<0.05
Radscore	6.959 (3.922–12.349)	<0.05	7.740 (3.560–16.800)	<0.05

OS, overall survival; BMI, body mass index; MVI, microvascular invasion; PV-TT, portal vein tumor thrombosis; platelet count; Radscore, radiomics score; HR, hazard ratio.

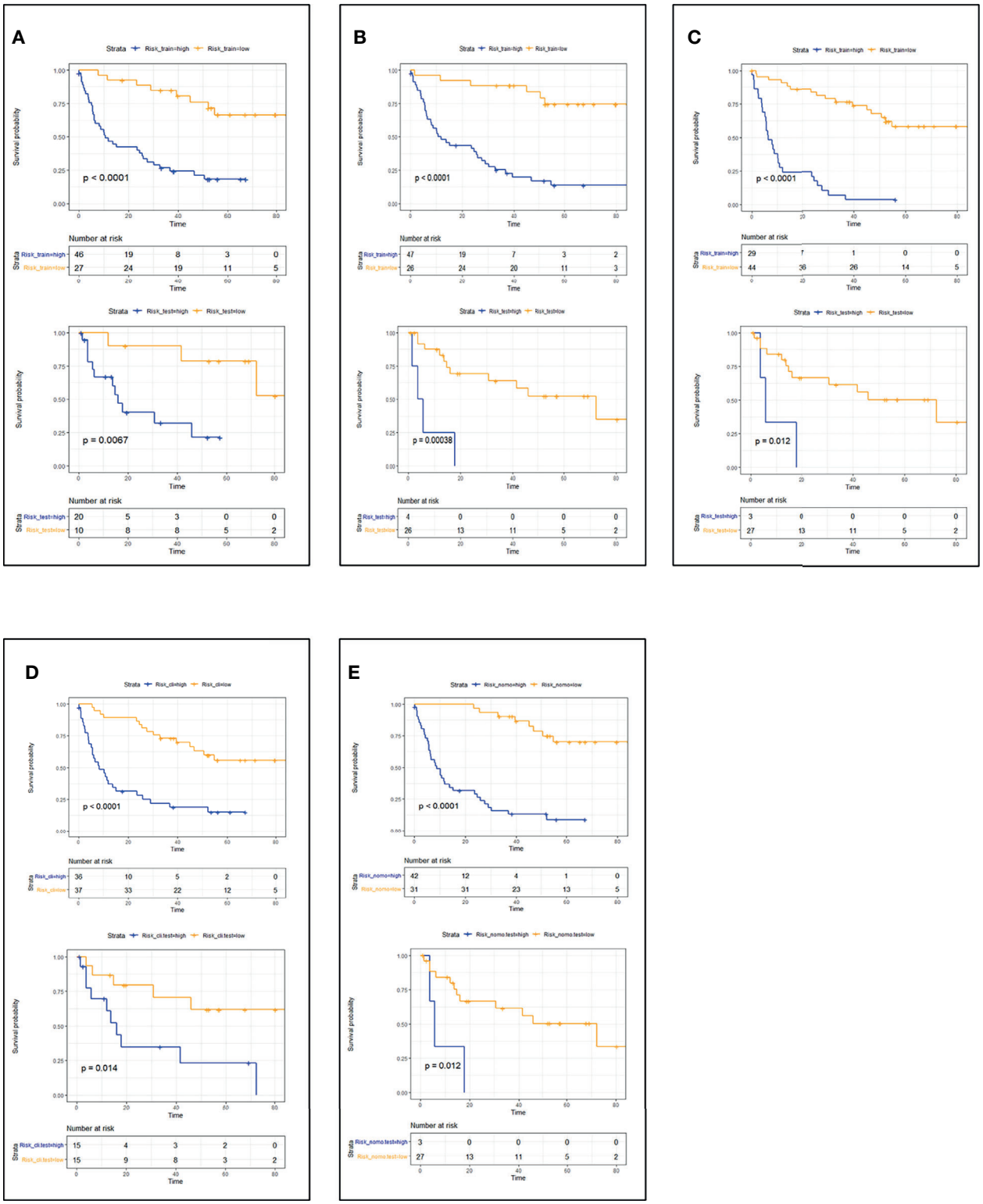

FIGURE 1 | Patient DFS KM curves for each model. **(A)** CT_DFS; **(B)** MRI_DFS; **(C)** CT+MRI_DFS; **(D)** Clinical_DFS; **(E)** CT+MRI+Clinical_DFS. *p*-Values were calculated using the log-rank test. Training cohort curves are shown on the top and validation cohorts on the bottom in each panel. DFS, disease-free survival; KM, Kaplan–Meier.

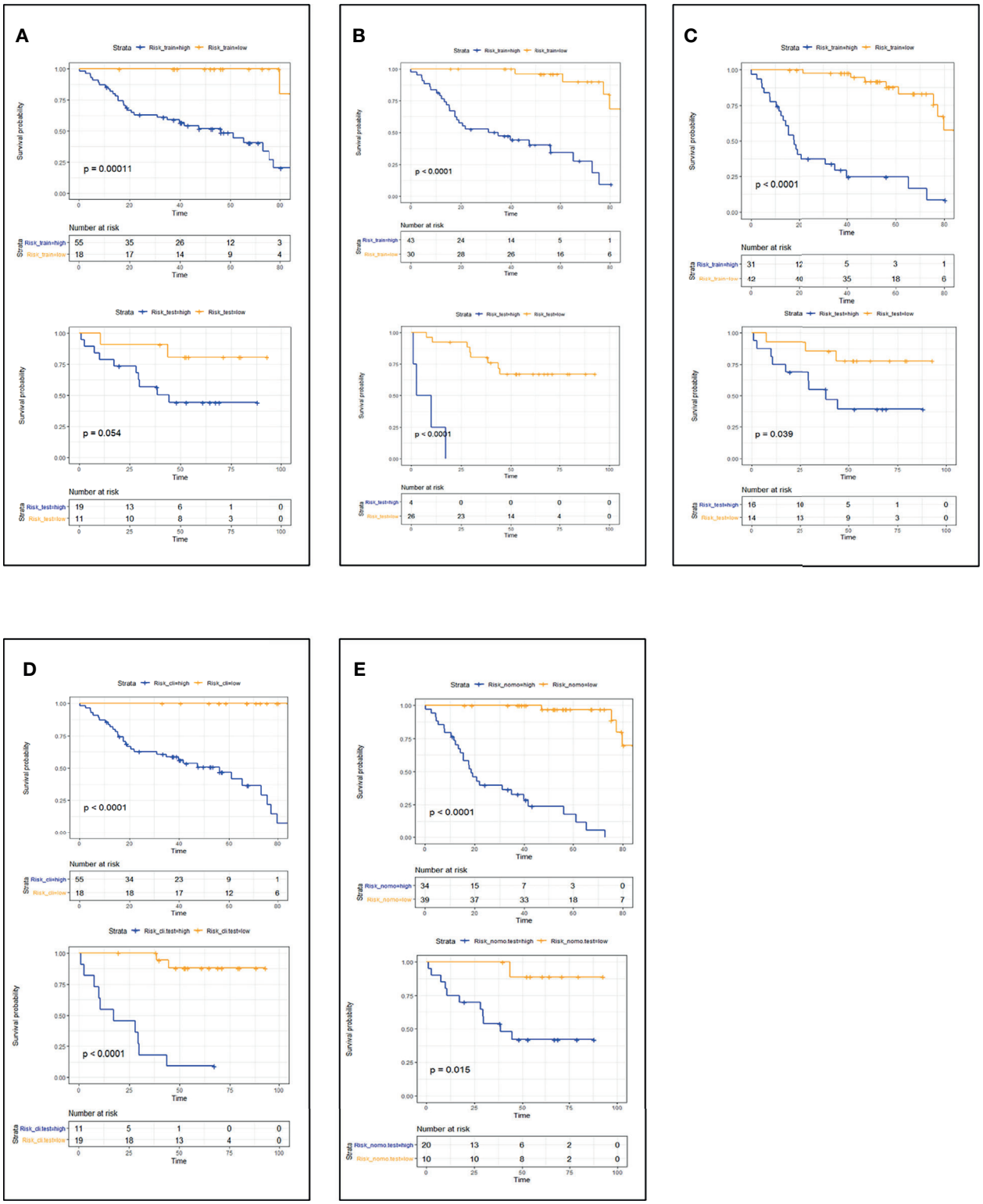

FIGURE 2 | Patient OS KM curves for each model: **(A)** CT_OS; **(B)** MRI_OS; **(C)** CT+MRI_OS; **(D)** Clinical_OS; **(E)** CT+MRI+Clinical_OS. *p*-Values were calculated using the log-rank test. Training cohort curves are shown on the top and validation cohorts on the bottom in each panel. OS, overall survival; KM, Kaplan–Meier.

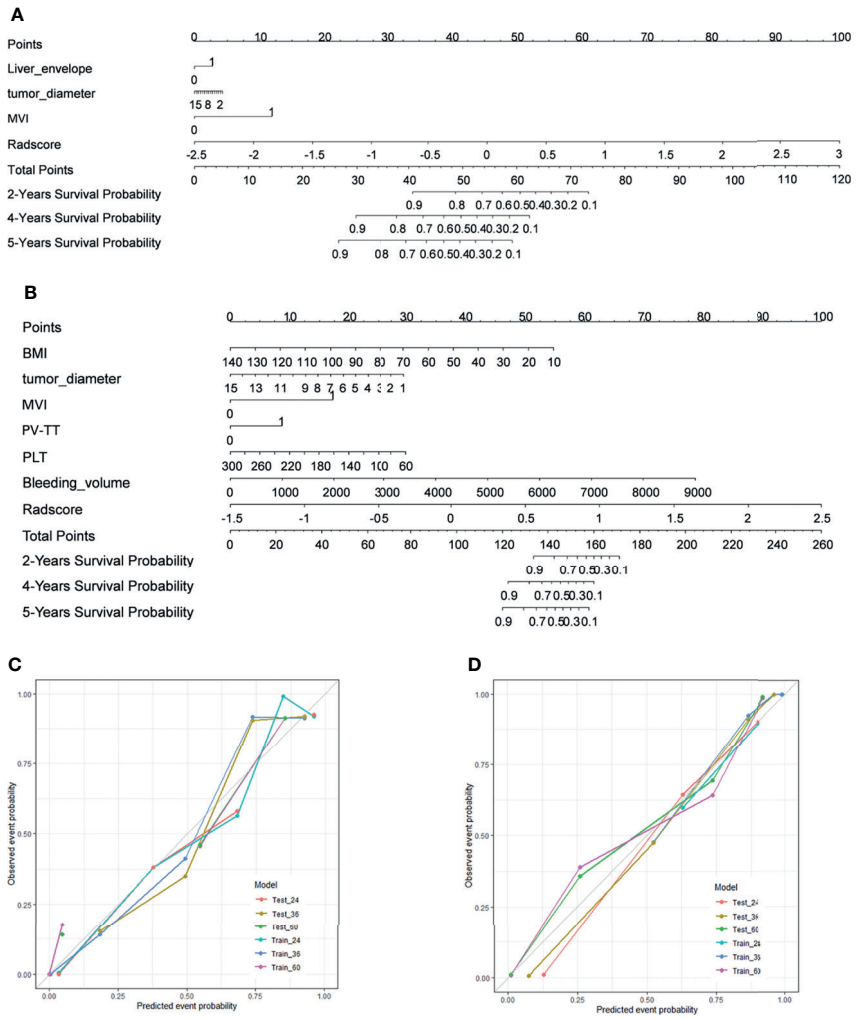

FIGURE 3 | Development of nomograms and calibration curves for DFS and OS in training cohorts. **(A)** Prognostic nomogram for DFS. **(B)** The prognostic nomogram for OS. **(C)** Calibration curves for DFS in the training cohort. **(D)** Calibration curves for OS in the training cohort. To determine the number of factors associated with the probability of survival, a straight line was drawn to the relevant point on the axis for each patient, and the process was repeated for each variable. Scores for each risk factor were then summarized, with the final sum marked on the overall point axis. DFS and OS estimated using the nomogram are plotted on the x-axis. Observed DFS or OS are plotted on the y-axis, and the estimated results are compared with the actual results. The consistency of estimated and observed calibrations for 2-year, 4-year, and 5-year survival results is shown for each model. DFS, disease-free survival; OS, overall survival.

TABLE 6 | The performance of each model in the training and validation cohorts.

	Model	Training cohort		Validation cohort	
Disease-free survival		C-index	95% CI	C-index	95% CI
	CT	0.742	0.668–0.816	0.614	0.442–0.786
	MRI	0.772	0.705–0.839	0.587	0.412–0.763
	CT+MRI	0.826	0.767–0.885	0.653	0.490–0.816
	Clinical	0.717	0.648–0.786	0.657	0.504–0.809
	CT+MRI+Clinical	0.858	0.811–0.905	0.704	0.563–0.845
Overall survival	CT	0.740	0.650–0.830	0.624	0.450–0.789
	MRI	0.833	0.768–0.898	0.601	0.401–0.801
	CT+MRI	0.865	0.810–0.920	0.653	0.471–0.835
	Clinical	0.802	0.714–0.890	0.705	0.597–0.803
	CT+MRI+Clinical	0.893	0.846–0.940	0.738	0.575–0.901

reflect information related to tumor heterogeneity, which are not visible to the human eye. Hence, radiomics can provide a non-invasive, low-cost, and reproducible means to capture tumor phenotypes that may be associated with intra-tumor heterogeneity (30). To date, radiomics has been used in research to explore liver tumors, including numerous studies applied to the diagnosis, prognosis, pathological grading, and MVI of liver cancer (31–34). Many previous studies have demonstrated the role of radiomics in survival assessment for patients with different types of cancer, including non-small cell lung, breast, and thyroid cancers (35–37).

We developed a new multimodal radiomics model to compare the value of enhanced CT and MRI sequence data for prognosis prediction in patients with HCC and to compare this with the predictive performance of clinicopathological factors. In this study, we extracted 1,217 features from CT and MR images and finally identified non-zero coefficient features associated with DFS and prognostic features associated with OS by LASSO regression analysis. Specific feature dimension reduction and features screening processes are also shown in the Supplementary Materials. Radscore values were calculated using these features. KM survival analysis methods and log-rank tests were used to evaluate their prognostic value.

In our study, the results of multivariate analyses showed that MVI, Bleeding_volume, and PLT were independent predictors of the prognosis of HCC patients, which was consistent with the results of previous studies (7–10). The CT+MRI+Clinical model was superior to that of a model comprising clinical features alone, CT alone, MRI alone, or CT+MRI combined model, indicating that the multimodal radiomics model approach may have a greater value in predicting DFS and OS of resected HCC. The multimodal model can provide more abundant information.

In addition, for all KM curves of predicting DFS and OS, the low-risk group had significantly higher survival times than the high-risk group ($p < 0.05$), indicating that Radscore was an independent predictor of HCC, and this finding was confirmed in the multivariate Cox proportional risk model ($p < 0.05$) in both DFS and OS. Thus, Radscore improves traditional prognostic ability and represents a potentially effective and promising tool for evaluating the prognosis of patients with HCC. This is consistent with the study by Zhao et al. (38). In a prior study, Zhang et al. (28) established single and multimodal logic models for predicting LVI, with excellent predictive power in training (area under the curve (AUC), 0.884; 95% CI, 0.803–0.964) and validation (AUC, 0.876; 95% CI, 0.721–1.000). Their results are similar to our study, but our model also included clinical factors. Univariate and multivariate Cox analyses were used to select clinical factors into the model to analyze the prognosis, which was more convincing and scientific by comparing the prediction performance of various modes, and it was shown in nomograms. Our Radscore-based nomograms yielded a better discriminative ability than these traditional methods for predicting prognosis in HCC patients.

Zhou et al. (24, 38) extracted radiomics features from arterial and portal phase CT images of 215 HCC patients undergoing partial hepatectomy, screened the imaging features through a LASSO logistic regression model, and constructed a Radscore model. The results showed that inclusion of CT-based radiomics features with routine clinical variables significantly predicted early recurrence (≤1 year) postoperatively and that the diagnostic performance of the model combining radiomics and clinical factors was superior to that of the model with clinical features alone for estimating early recurrence. It seems to be obvious that assessing tumorous disease with single modal radiomics information will not be comprehensive. However, the development of methods and strategies for the integration of information of different dimensions is still in its early stages, and combining prediction models, as performed in the current study, might increase their precision and could be extended to other diagnostic indicators. Further research following this scheme is warranted.

This study has several limitations. First, our study was conducted in a single institution. Although all CT and MR images were obtained using a uniform scanner and standardized imaging acquisition sequences, to reduce bias and variance in our results and improve the robustness of the model, further confirmation using patient data from other institutions is needed. Second, the use of manually drawn two-dimensional ROI is time-consuming and inconvenient for clinical application; hence, the feasibility of automatic segmentation or semi-segmentation in radiomics analysis will be the focus of future research. Third, the number of patients in this study is not large because not all HCC patients need to undergo CT and MR in clinical practice. In addition, the cost of conducting CT and MR at the same time is relatively expensive, so there are some obstacles to implementation. Finally, our single-center study primarily included patients who had undergone CT and MR, with a small sample size. We will work with other hospitals to explore the robustness of similar multimodal models in the future.

In conclusion, our results suggest that Radscore is an independent prognostic factor in patients with HCC. Multimodal imaging profiles have great potential to improve individualized assessment of likely prognosis after surgery and may guide the individualized care of patients with HCC.

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 Affiliated Hospital of Qingdao University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YH, CZ, QD, BH, and XZ contributed to the conception and design. YH, BH, WX, and XC organized the database. YG, XH, and BD managed the patient and provided technical support. YH wrote the first draft of the manuscript. YH and YG performed the statistical analysis, CZ, QD, and XZ reviewed and revised the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.2022.745258/full#supplementary-material

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Conflict of Interest: YG was employed by GE Healthcare.

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ORIGINAL RESEARCH
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Development and Validation of a Prognostic Model to Predict Recurrence-Free Survival After Curative Resection for Perihilar Cholangiocarcinoma: A Multicenter Study

Zhi-Peng Liu[1], Wei-Yue Chen[2], Zi-Ran Wang[3], Xing-Chao Liu[4], Hai-Ning Fan[5], Lei Xu[1], Yu Pan[1], Shi-Yun Zhong[1], Dan Xie[1], Jie Bai[1], Yan Jiang[1], Yan-Qi Zhang[6], Hai-Su Dai[1] and Zhi-Yu Chen[1]**

[1] Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China, [2] Department of Clinical Research Institute, Lishui Hospital of Zhejiang University, Lishui, China, [3] Department of General Surgery, 903rd Hospital of People's Liberation Army, Hangzhou, China, [4] Department of Hepatobiliary Surgery, Sichuan Provincial People's Hospital, Chengdu, China, [5] Department of Hepatobiliary Surgery, Affiliated Hospital of Qinghai University, Xining, China, [6] Department of Health Statistics, College of Military Preventive Medicine, Third Military Medical University (Army Medical University), Chongqing, China

Background: Recurrence is the main cause of death in perihilar cholangiocarcinoma (pCCA) patients after surgery. Identifying patients with a high risk of recurrence is important for decision-making regarding neoadjuvant therapy to improve long-term outcomes.

Aim: The objective of this study was to develop and validate a prognostic model to predict recurrence-free survival (RFS) after curative resection of pCCA.

Methods: Patients following curative resection for pCCA from January 2008 to January 2016 were identified from a multicenter database. Using random assignment, 70% of patients were assigned to the training cohort, and the remaining 30% were assigned to the validation cohort. Independent predictors of RFS after curative resection for pCCA were identified and used to construct a prognostic model. The predictive performance of the model was assessed using calibration curves and the C-index.

Results: A total of 341 patients were included. The median overall survival (OS) was 22 months, and the median RFS was 14 months. Independent predictors associated with RFS included lymph node involvement, macrovascular invasion, microvascular invasion, maximum tumor size, tumor differentiation, and carbohydrate antigen 19-9. The model incorporating these factors to predict 1-year RFS demonstrated better calibration and better

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Alessandro Vitale,
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Jose M. Ramia,
Hospital General Universitario de Alicante, Spain
Tommaso Stecca,
ULSS2 Marca Trevigiana, Italy

***Correspondence:**
Zhi-Yu Chen
chenzhiyu_umn@163.com
Hai-Su Dai
daihaisu@163.com

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performance than the 8th American Joint Committee on Cancer (AJCC) staging system in both the training and validation cohorts (C-indexes: 0.723 *vs.* 0.641; 0.743 *vs.* 0.607).

Conclusions: The prognostic model could identify patients at high risk of recurrence for pCCA to inform patients and surgeons, help guide decision-making for postoperative adjuvant therapy, and improve survival.

Keywords: perihilar cholangiocarcinoma, prognostic model, recurrence, resection, oncology

INTRODUCTION

Cholangiocarcinoma (CCA) is an epithelial tumor with features of cholangiocyte differentiation. It originates from the ductal epithelium of the biliary tree from the canals of Hering to the main bile duct, and although it accounts for only 3% of gastrointestinal tumors, the incidence has gradually increased in the past decade (1, 2). According to the anatomical location, 60%-70% of cholangiocarcinomas are perihilar (3, 4). While curative resection is the recommended treatment for perihilar cholangiocarcinoma (pCCA), the 5-year overall survival (OS) is very poor, at only 25%-35%, and recurrence is the main cause of death (5, 6). Thus, screening out pCCA patients with a high risk of recurrence after curative resection has become a critical step.

At present, the 8th American Joint Committee on Cancer (AJCC) TNM has been proposed to predict oncologic outcomes for patients. However, it lacks accuracy because AJCC staging lacks many prognostic factors (7). With the deepening of the studies, most of the factors related to prognosis after curative pCCA resection have been determined, including tumor differentiation, macro- or microvascular invasion, tumor size, lymph node (LN) status, and serum tumor biomarkers (8–12). For LN status, provided that the number of examined lymph nodes (ELNs) is less than 4, prediction systems may falsely indicate negative LN involvement, which was demonstrated to be an independent risk factor for poor oncologic prognosis of pCCA (13–15). For tumor size, patients with tumor size > 3 cm have a poorer prognosis (16). Moreover, tumor size > 5 cm was also found to be related to poor survival of pCCA (17). Based on these studies, it may be possible to refine the tumor size to more accurately predict the long-term prognosis of pCCA patients. Notably, in the past 5 years, several studies have developed models to predict the long-term prognosis of pCCA, but all of them lack serum tumor biomarkers (18–21). Carbohydrate antigen 19-9 (CA 19-9) is a known serum tumor biomarker that is independently associated with the long-term prognosis of pCCA (22). As a consequence, this study tried to add the above mentioned variables to one prognostic model may further improve the prediction performance of individual patients after curative pCCA resection. Despite that, predicting the long-term oncologic outcomes of individual patients remains challenging. A nomogram is a visual and simple prognostic model system that can predict the long-term outcome of individual patients based on various prognostic parameters. In recent years, nomograms have been proven to be more accurate than traditional cancer staging systems for the prediction of malignant gastrointestinal tumors such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma (23, 24).

All of the previous studies published to predict the prognosis of pCCA have only focused on the death of patients but have ignored recurrence. As a consequence, a more accurate prognostic model of individual pCCA patients can screen out the population of high-risk recurrence so that postoperative preventive adjuvant therapy can be more recommended. In particular, using a multicenter database, the object of this study was to develop and validate a prognostic model to predict recurrence-free survival (RFS) after curative pCCA resection.

Abbreviations: ALB, albumin; ALT, alanine aminotranferase; AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; AUC, area under the curve; CA19-9, Carbohydrate antigen 19-9; CCA, cholangiocarcinoma; CI, confidence interval; C-index, Concordance index; CT, computed tomography; DCA, decision curve analysis; ELN, examined lymph nodes; HR, hazard ratio; INR, international normalized ratio; LN, lymph node; MRI, magnetic resonance imaging; OS, overall survival; pCCA, perihilar cholangiocarcinoma; RFS, recurrence-free survival; PLT, platelet; ROC, receiver operating characteristic; SEER, epidemiology and end results; TB, total bilirubin; WMA, World Medical Association.

METHODS

Study Population

This is a retrospective study. Following open curative resection for newly diagnosed pCCA between January 2008 and January 2016 at three hospitals in China, patients were enrolled in a multicenter database (Southwest Hospital, Sichuan Provincial People's Hospital, and Affiliated Hospital of Qinghai University). The diagnosis of pCCA was confirmed by postoperative histological examination. Patients with tumors emerging from the biliary confluence, right or left hepatic duct, or common hepatic duct were included in the study. The exclusion criteria were as follows: 1) recurrent pCCA; 2) neoadjuvant therapy; 3) palliative resection (R1 & R2 resection); 4) no liver resection; 5) death within 30 days after surgery; 6) missing data on important prognostic variables, including CA 19-9, maximum tumor size, macrovascular or microvascular invasion, tumor differentiation, and LN involvement; and 7) loss to follow-up. All patients underwent hepatectomy and extrahepatic bile duct resection. Regardless of whether the preoperative radiology examination suspects lymph node involvement, all patients underwent locoregional lymphadenectomy, including 8, 9, 12, and 16 stations of lymph nodes (LNs). To achieve

curative resection, patients received hepatectomy-pancreaticoduodenectomy and/or revascularization when required. Patients received revascularization when the vasculature of the reserved side liver was violated. Curative resection was defined as complete resection of all microscopic and macroscopic pCCA tumors with microscopically clear resection margins in the surgical specimens. Using random assignment, 70% of patients were assigned to a training cohort, and the remaining 30% were assigned to the validation cohort. This study followed the ethical guidelines of the WMA (World Medical Association; Declaration of Helsinki). Approval for this study research was obtained from the Ethics Committee of Southwest Hospital (approval number: KY2021129). All patients provided written informed consent prior to participation in this clinical study.

Data Collection

Clinical, laboratory, pathological and surgical variables were recorded for all patients. Clinical variables included age, sex, American Society of Anesthesiologists (ASA) score, diabetes mellitus, obesity, and preoperative drainage. Laboratory variables included alanine aminotransferase (ALT), aspartate transaminase (AST), platelets (PLT), albumin (ALB), total bilirubin (TB), international normalized ratio (INR), and carbohydrate antigen 19-9 (CA 19-9). Pathological variables included cirrhosis, maximum tumor size, macrovascular invasion, microvascular invasion, peripheral nerve invasion, tumor differentiation, 8th AJCC stage, Bismuth classification, and LN involvement. Surgical variables included perioperative blood transfusion, intraoperative blood loss, extent of hepatectomy (minor and major), and number of examined LNs (ELN).

For laboratory variables, we used the upper or lower limit of the normal values in clinical practice to divide patients into normal or high/low groups, including 40 U/L for ALT and AST, 100×10^9/L for PLT, 35 g/L for ALB, 1 mg/dL for TB, and 1.25 for INR. Based on the previous studies, although 37 U/L is the upper limit of the normal value of CA199, to obtain the strongest predictive value, this study used 150 U/L as the cutoff value for CA19-9 (25, 26). Cirrhosis was confirmed by postoperative histological examination of the noncancerous resected specimen. Maximum tumor size, macrovascular invasion, microvascular invasion, peripheral nerve invasion, tumor differentiation, and LN involvement were confirmed by postoperative histological examination of the cancerous resected specimen. Tumor stage and categorization were determined according to the 8th AJCC stage and Bismuth classification (27, 28). Tumor size > 3 cm is commonly considered to be a factor leading to a poor prognosis. This study used 3 and 5 cm to divide all patients into three groups. In addition, this study divided the lymph node status into three groups: positive, negative (ELN < 4), and negative (ELN ≥ 4). Minor hepatectomy was defined as the resection of two or fewer Couinaud liver segments, and major hepatectomy was defined as the resection of three or more segments.

Patient Follow-Up

All patients were followed up at regular intervals (approximately 1-2 months) after discharge. A standard protocol was used to evaluate the presence of pCCA recurrence, which included clinical symptoms, laboratory (tumor biomarkers and liver function), physical examinations, and radiographic images. One abdominal contrast-enhanced ultrasound (CEUS), computed tomography (CT), or magnetic resonance imaging (MRI) was performed every two months after surgery or when tumor recurrence was suspected. The presence of new lesions seen on CEUS, CT or MRI was defined as recurrence that was treated by further treatment. The primary endpoint was recurrence-free survival (RFS), and the secondary endpoint was overall survival (OS). For recurrent patients, RFS was defined as the interval from surgery to the diagnosis of tumor recurrence. For nonrecurrent patients, RFS was defined as the interval from surgery to death or last follow-up. OS was defined as the interval from surgery to death or last follow-up. The database was censored on November 15, 2020.

Statistical Analysis

Categorical variables are expressed as numbers and percentages. The χ^2 test or Fisher's exact test was used as appropriate. RFS was assessed using the Kaplan–Meier method. Univariable and multivariable analyses were performed using Cox regression with forward stepwise variable selection to identify factors to predict RFS. Variables significant at a P value < 0.1 in univariable analysis were entered into multivariable Cox regression analysis. The algorithm used in choosing factors for the nomogram was based on independent variables associated with RFS on multivariable Cox regression analysis to construct the nomogram model, which was formulated in R for predicting the probability of 1-, 3-, and 5-year RFS. The nomogram was subjected to 1,000 bootstrap resamples for internal validation. The performance of the nomogram in predicting survival was evaluated by calculating the area under the curve (AUC) and concordance index (C-index). To assess the fit of the nomogram, the nomogram was calibrated by comparing the predicted RFS with the observed RFS after bias correction. The clinical validity of the nomogram was evaluated by decision curve analysis (DCA), which calculated the true and false positive rates of various risk thresholds and compensated for any deficiency of ROC curves (receiver operating characteristic curves) (29). The difference in predictive performance between the nomogram and 8th AJCC stage was assessed with ROC curve analysis and DCA. Based on the median nomogram score of the patients in the training cohort, all patents were divided into a low-risk group and a high-risk group. The statistical analysis was performed using SPSS 26.0 (SPSS, Chicago, IL, USA) and R software (version 3.5.1. http://www.r-project.org/). An internet browser-based calculator based on the nomogram model was programmed in JavaScript. A P value < 0.05 was considered to indicate a significant difference in a 2-tailed test.

RESULTS

Patients and Variables

Among the 523 patients who underwent curative open resection for pCCA between January 2008 and January 2016, we excluded 15 patients who had recurrent pCCA, 30 patients who received neoadjuvant therapy, 25 patients who underwent palliative resection (R1 & R2), 26 patients who did not undergo liver resection, and 11 patients who died within 30 days after surgery. Moreover, 36 patients who had missing data on important prognostic variables and 39 patients who were lost to follow-up were also excluded. Thus, 341 patients with newly diagnosed pCCA were included in the final analytic cohort (210 male and 131 female patients), and 27.0% of patients were older than 60 years old. Among the 341 patients in the whole cohort, 239 (70.1%) patients were randomly assigned to the training cohort, and 102 (29.9%) patients were allocated to the validation cohort, as shown in **Supplementary Figure 1**. The clinical, laboratory, pathological and surgical variables among patients in the training and validation cohorts are shown in **Table 1**. The median OS and RFS times for the whole cohort of patients were 22.0 (95% CI: 18.9-25.1) and 14.0 (95% CI: 11.1-16.8) months, respectively. The 1-, 3-, and 5-year RFS rates in the whole cohort of patients were 53.4%, 25.0%, and 17.4%, respectively. The 1-, 3-, and 5-year OS rates in the whole cohort of patients were 70.9%, 32.6%, and 23.3%, respectively. The survival outcomes of the training and validation cohorts are shown in **Table 2**.

Predictors of RFS and Development of the Nomogram Model

On univariable and multivariable Cox regression analyses, six variables were independently associated with RFS for pCCA, as shown in **Table 3**, including CA 19-9 (> 150 *vs.* ≤ 150 U/L) (HR: 1.601, 95% CI: 1.162-2.206); maximum tumor size (3~5 *vs.* < 3 cm) (HR: 1.688, 95% CI: 1.217-2.340), maximum tumor size (> 5 *vs.* < 3 cm) (HR: 1.926, 95% CI: 1.178-3.147); macrovascular invasion (yes *vs.* no) (HR 1.629, 95% CI: 1.198-2.216); microvascular invasion (yes *vs.* no) (HR: 1.566, 95% CI: 1.066-2.300); tumor differentiation (poor *vs.* well/moderate) (HR: 1.635, 95% CI: 1.082-2.470); LN involvement [no (ELN ≤ 4) *vs.* no (ELN > 4)] (HR: 1.340, 95% CI: 0.889-2.020), LN involvement [yes *vs.* no (ELN > 4)] (HR: 2.421, 95% CI: 1.605-3.652). A nomogram model that enrolled these six independent risk factors for RFS for pCCA was constructed, as shown in **Figure 1A**. Each variable was assigned a score on a point scale. By adding the scores of each variable, locating the total score on the total score table, and drawing a straight line down vertically, the probability of 1-, 3-, and 5-year RFS could be determined. In addition, the model was made *via* a free browser-based model, which is available at https://wangyeliexiantu.shinyapps.io/DynNomapp/, as shown in **Figure 1B**. The prognostic model demonstrated good calibration for risk estimation in the training cohort, as shown in **Figure 2A**. The nomogram also demonstrated good performance in predicting the probability of 1-year RFS, with an AUC of 0.769 (95% CI: 0.708–0.829) in the training cohort, as shown in **Figure 2B**.

TABLE 1 | Patients' characteristics for perihilar cholangiocarcinoma.

Variables	Whole cohort (N = 341)	Training cohort (N = 239)	Validation cohort (N = 102)
Age (years), ≤ 60/> 60	249/92 (73.0/27.0)	176/63 (73.6/26.4)	73/29 (71.6/28.4)
Gender, Female/Male	131/210 (38.4/61.6)	96/143 (40.2/59.8)	35/67 (38.4/61.6)
ASA score > 2	27 (7.9)	19 (7.9)	8 (7.8)
Diabetes mellitus	31 (9.1)	20 (8.4)	11 (10.8)
Obesity	59 (17.3)	40 (16.7)	19 (18.6)
Preoperative drainage, No/Yes	230/111 (67.4/32.6)	164/75 (68.6/31.4)	66/36 (64.7/35.3)
ALT (U/L), ≤ 40/> 40	52/289 (15.2/84.8)	36/203 (15.1/84.9)	16/86 (15.7/84.3)
AST (U/L), ≤ 40/> 40	49/292 (14.4/85.6)	33/206 (13.8/86.2)	16/86 (15.7/84.3)
PLT ($\times10^9$/L), ≥ 100/≤ 100	325/16 (95.3/4.7)	228/11 (95.4/4.6)	97/5 (95.1/4.9)
ALB (g/L), ≥ 35/≤ 35	223/118 (65.4/34.6)	159/80 (66.5/33.5)	64/38 62.7/37.3)
TB (mg/dL), ≤ 1/> 1	69/272 (20.2/79.8)	46/193 (19.2/80.8)	23/79 (22.5/77.5)
INR, ≤ 1.25/> 1.25	293/48 (85.9/14.12)	208/31 (87.0/13.0)	85/17 (83.3/16.7)
CA 19-9 (U/L), ≤ 150/> 150	147/194 (43.1/56.9)	106/133 (44.4/55.6)	41/61 (40.2/59.8)
Cirrhosis	28 (8.2)	20 (8.4)	8 (7.8)
Maximum tumor size (cm), < 3/3-5/> 5	152/159/30 (44.6/45.6/8.8)	106/111/22 (44.4/46.4/9.2)	46/48/8 (45.1/47.1/7.8)
Macrovascular invasion, No/Yes	187/154 (54.8/45.2)	130/109 (54.4/45.6)	57/45 (55.9/44.1)
Microvascular invasion, No/Yes	285/56 (83.6/16.4)	198/41 (82.8/17.2)	87/15 (85.3/14.7)
Peripheral nerve invasion, No/Yes	216/125 (63.3/36.7)	153/86 (64.0/36.0)	63/39 (61.8/38.2)
Tumor differentiation, Well/moderate/Poor	286/55 (83.9/16.1)	201/38 (84.1/15.9)	85/17 (83.3/16.7)
8th AJCC stage, I-II/III-IV	121/220 (35.5/64.5)	91/148 (38.1/61.9)	30/72 (29.4/70.6)
Bismuth classification, I-II/III-IV	71/270 (20.8/79.2)	52/187 (21.8/78.2)	19/83 (18.6/81.4)
Lymph node involvement, No (ELN > 4)/No (ELN ≤ 4)/Yes	82/128/131 (24.0/37.5/38.4)	59/90/90 (24.7/37.7/37.7)	23/38/41 (22.5/37.3/40.2)
Perioperative blood transfusion, No/Yes	115/226 (33.7/66.3)	83/156 (34.7/65.3)	32/70 (31.4/68.6)
Intraoperative blood loss (ml), ≤ 500/> 500	127/214 (37.2/62.8)	90/149 (37.7/62.3)	37/65 (36.3/63.7)
Extent of hepatectomy, Minor/Major	107/234 (31.4/68.6)	78/161 (32.6/67.4)	29/73 (28.4/71.6)

AJCC, American Joint Committee on Cancer; ALB, albumin level; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA19-9, carbohydrate antigen 19-9; INR, international normalized ratio; PLT, platelets level; TB, total bilirubin.

TABLE 2 | Survival outcomes for perihilar cholangiocarcinoma.

Survival outcomes	Whole cohort (N = 341)	Training cohort (N = 239)	Validation cohort (N = 102)
Period of follow-up, months*	25.7 ± 23.4	25.7 ± 22.7	26.0 ± 25.0
Recurrence during the follow-up	255 (74.8)	180 (75.3)	75 (73.5)
Death during the follow-up	231 (67.7)	163 (68.2)	68 (66.7)
OS, months**	22.0 (18.9-25.1)	23.0 (19.2-26.8)	19.0 (12.3-25.7)
1-year OS rate, %	70.9	72.6	67.1
3-year OS rate, %	32.6	32.2	33.3
5-year OS rate, %	23.3	21.9	26.4
RFS, months**	14.0 (11.1-16.8)	16.0 (12.5-19.5)	13.0 (6.5-19.5)
1-year RFS rate, %	53.4	54.8	50.1
3-year RFS rate, %	25.0	24.6	25.9
5-year RFS rate, %	17.4	15.8	21.0

**Values are mean ± standard deviation. **Values are median and 95% confidence interval.*
OS, overall survival; RFS, recurrence-free survival.

Validation and Clinical Applicability

The prognostic model calibration demonstrated similarly a good fit in the validation cohort, and the prediction for the probability of 1-year RFS agreed with actual observations, as shown in **Figure 2C**. Meanwhile, the nomogram performed similarly well when applied to the validation cohort to predict the probability of 1-year RFS for pCCA, with an AUC of 0.813 (95% CI: 0.728–0.898), as shown in **Figure 2D**.

DCA demonstrated that using this prognostic model to predict the probability of 1-year RFS provided more benefit than the 8th AJCC stage in both the training and validation cohorts, as shown in **Figure 3A**, **B**, respectively. In addition, the nomogram model had a higher AUC than the 8th AJCC stage for predicting 1-year RFS in the training and validation cohorts, as shown in **Figure 3C**, **D**, respectively. In the training cohort, the discriminatory ability of the prognostic model had a C-index of 0.723 (95% CI: 0.684-0.762), which was superior to the 8th AJCC stage (C-index: 0.641, 95% CI: 0.576-0.706). In the validation cohort, the discriminatory ability of the prognostic model had a C-index of 0.743 (95% CI: 0.688-0.798), which was superior to the 8th AJCC stage (C-index: 0.607, 95% CI: 0.503-0.711). Notably, the prognostic model also performed better than the

TABLE 3 | Univariable and multivariable Cox regression analyses for RFS of the training cohort.

Variables		Univariable analyses		Multivariable analyses*	
		P	HR (95% CI)	*P*	HR (95% CI)
Age	> 60 *vs.* ≤ 60 years	.303	1.185 (0.858-1.636)		
Gender	Male *vs.* Female	.386	0.877 (0.652-1.180)		
ASA score	> 2 *vs.* ≤ 2	.253	1.350 (0.807-2.259)		
Diabetes mellitus	Yes *vs.* No	.397	1.234 (0.758-2.010)		
Obesity	Yes *vs.* No	.995	1.001 (0.679-1.476)		
Preoperative drainage	Yes *vs.* No	.772	1.059 (0.773-1.450)		
ALT	> 40 *vs.* ≤ 40 U/L	.346	1.222 (0.805-1.856)		
AST	> 40 *vs.* ≤ 40 U/L	.583	1.131 (0.730-1.752)		
PLT	< 100 *vs.* ≥ 100 $\times 10^9$/L	.573	1.226 (0.603-2.494)		
ALB	< 35 *vs.* ≥ 35 g/L	.490	1.116 (0.818-1.522)		
TB	> 1 *vs.* ≤ 1 mg/dL	.712	1.074 (0.735-1.571)		
INR	> 1.25 *vs.* ≤ 1.25	.807	1.058 (0.671-1.669)		
CA 19-9	> 150 *vs.* ≤ 150 U/L	<.001	1.931 (1.426-2.616)	.004	1.601 (1.162-2.206)
Cirrhosis	Yes *vs.* No	.647	1.128 (0.674-1.885)		
Maximum tumor size	3-5 *vs.* < 3 cm	<.001	2.154 (1.566-2.961)	.002	1.688 (1.217-2.340)
	> 5 vs. < 3 cm	.013	1.840 (1.135-2.982)	.009	1.926 (1.178-3.147)
Macrovascular invasion	Yes *vs.* No	<.001	1.948 (1.445-2.625)	.002	1.629 (1.198-2.216)
Microvascular invasion	Yes *vs.* No	.002	1.836 (1.261-2.672)	.022	1.566 (1.066-2.300)
Peripheral nerve invasion	Yes *vs.* No	.748	1.051 (0.776-1.424)		
Tumor differentiation	Poor *vs.* Well/moderate	.009	1.691 (1.138-2.514)	.020	1.635 (1.082-2.470)
Lymph node involvement	No (ELN ≤ 4) *vs.* No (ELN > 4)	.066	1.460 (0.975-2.186)	.162	1.340 (0.889-2.020)
	Yes *vs.* No (ELN > 4)	<.001	2.713 (1.818-4.049)	<.001	2.421 (1.605-3.652)
Perioperative blood transfusion	Yes *vs.* No	.528	1.106 (0.809-1.510)		
Intraoperative blood loss (ml)	> 500 *vs.* ≤ 500 ml	.358	1.154 (0.850-1.566)		
Extent of hepatectomy	Major *vs.* Minor	.518	1.108 (0.811-1.514)		

**Those variables found significant at P <.100 in univariable analyses were entered into multivariable Cox regression analyses.*
ALB, albumin level; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; PLT, platelets level; RFS, recurrence-free survival; TB, total bilirubin.

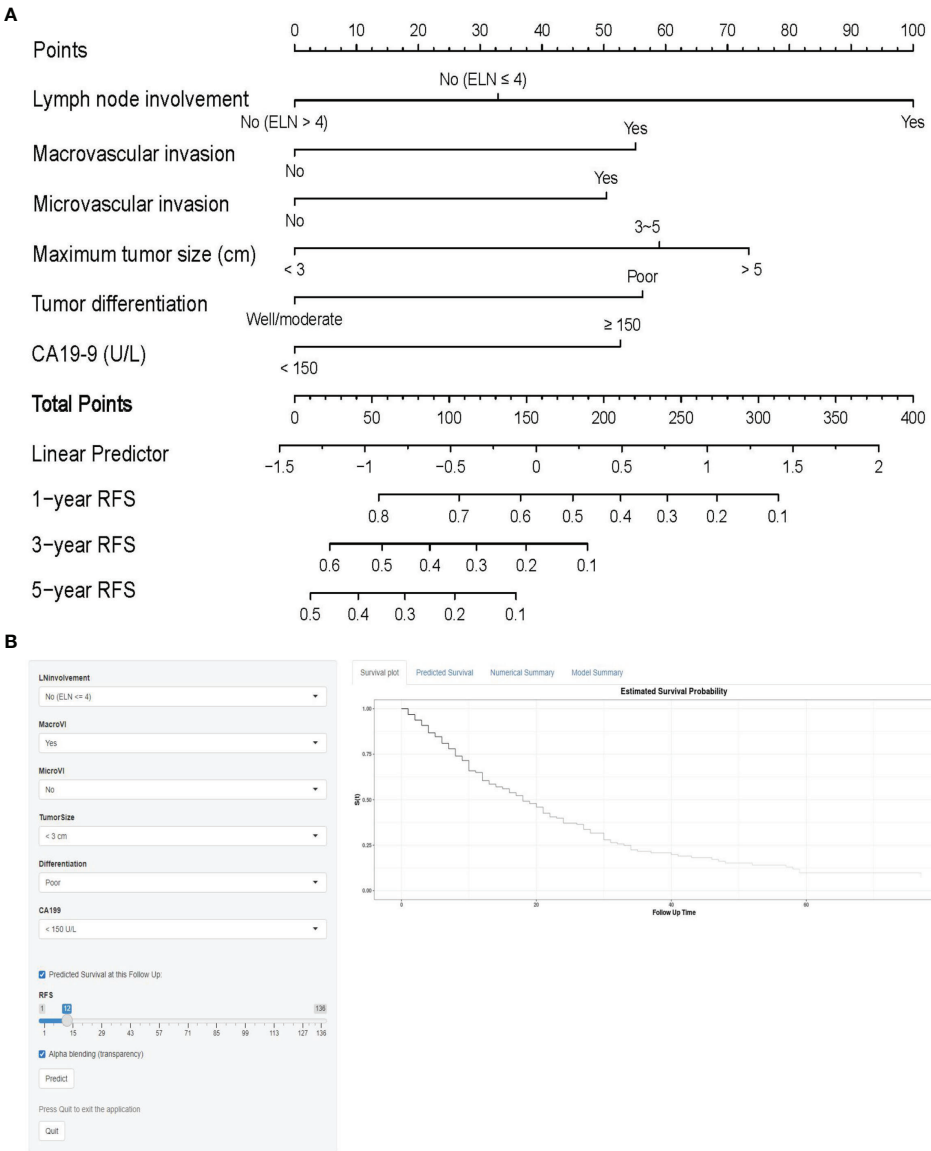

FIGURE 1 | Prognostic model **(A)** and online model **(B)** for the prediction of 1-, 3-, and 5-year RFS for perihilar cholangiocarcinoma. CA19-9, carbohydrate antigen 19-9; ELN, total number of lymph nodes examined; RFS, recurrence-free survival.

8th AJCC stage for the prediction of 1-year OS in both the training and validation cohorts, as shown in **Table 4**.

Risk Group Stratification Based on the Nomogram Score

The median model score of the training cohort, 159, effectively distinguished populations of different recurrence risks in the training and validation cohorts. Patients with a model score > 159 had a high risk of recurrence, and patients with a model score ≤ 159 had a low risk of recurrence. The formula for calculating the model score is shown in **Supplementary Table 1**. The RFS of high-risk patients was inferior to that of low-risk patients in both the training and validation cohorts, as shown in **Figures 4A**, **B**, respectively. In addition, the OS of high-risk patients was inferior to that of low-risk patients in both the training and validation cohorts, as shown in **Figures 4C**, **D**, respectively.

DISCUSSION

Traditionally, Bismuth-Corlette, Memorial Sloan-Kettering Cancer Center, and Blumgart staging systems are mostly used to evaluate the respectability of pCCA according to the tumor location in the biliary tree, portal vein invasion, and liver lobe atrophy status (30). According to the abovementioned stage, clinical surgeons are able to choose the most suitable surgical

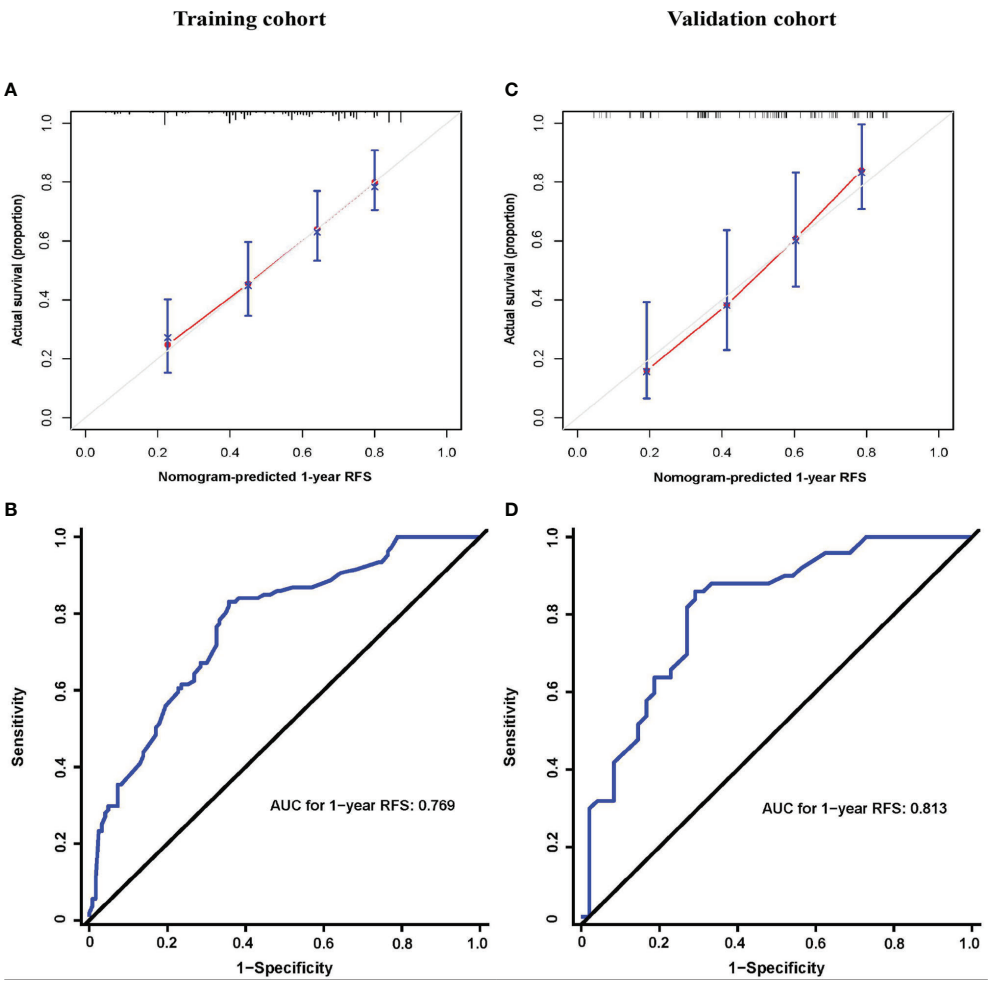

FIGURE 2 | Prognostic model properties. Calibration **(A, C)** and ROC curves **(B, D)** of the prognostic model for the training **(A, B)** and validation cohorts **(C, D)**. AJCC, American Joint Committee on Cancer; AUC, area under curve; RFS, recurrence-free survival.

methods (30). After curative surgery, tumor recurrence is the main cause of death in pCCA patients, so clinicians urgently need a tool that can accurately predict recurrence. An effective prediction of the long-term oncologic prognosis can not only be used to refer to the frequency and duration of follow-up needed but can also provide a basis for further adjuvant treatment after surgery. However, little attention has been given to stage when evaluating the patient's prognosis after surgery. The AJCC TNM is a widely used staging system that can not only guide the preoperative treatment plan but also predict the postoperative prognosis of patients (7). Unfortunately, the AJCC TNM staging only includes the indicators of the tumor itself, so it is not accurate enough in predicting long-term survival (7). The nomogram is a visual and simple model that is able to predict the survival outcome in various tumors and has been widely used in clinical practice due to its feasibility and accuracy (31–33). Thus, in this study, an online prognostic model was developed and validated to predict RFS after curative resection of pCCA. The model was presented as a nomogram and an online model, and the analysis results showed that the model had excellent predictive performance, with a C-index of 0.723 in the training cohort and 0.743 in the validation cohort. Calibration was also excellent in both the training and validation cohorts. This prognostic model clearly outperformed the 8th AJCC TNM staging system.

This prognostic model was based on six independent risk factors that are present in the histology and serum tumor biomarker report of every resected pCCA, including LN involvement and count, macro- and microvascular invasion, maximum tumor size, tumor differentiation, and CA 19-9. LN involvement is commonly considered to be an independent predictor for poorer oncologic prognosis in pCCA patients (34). Notably, when positive LNs are not found, the examination of less than four LNs can cause understaging and is independently associated with poor prognosis (13). For tumors of the biliary system, lymphatic metastasis is a very important dissemination method for metastasis. Therefore, we believe that pCCA patients, regardless of whether imaging suggests

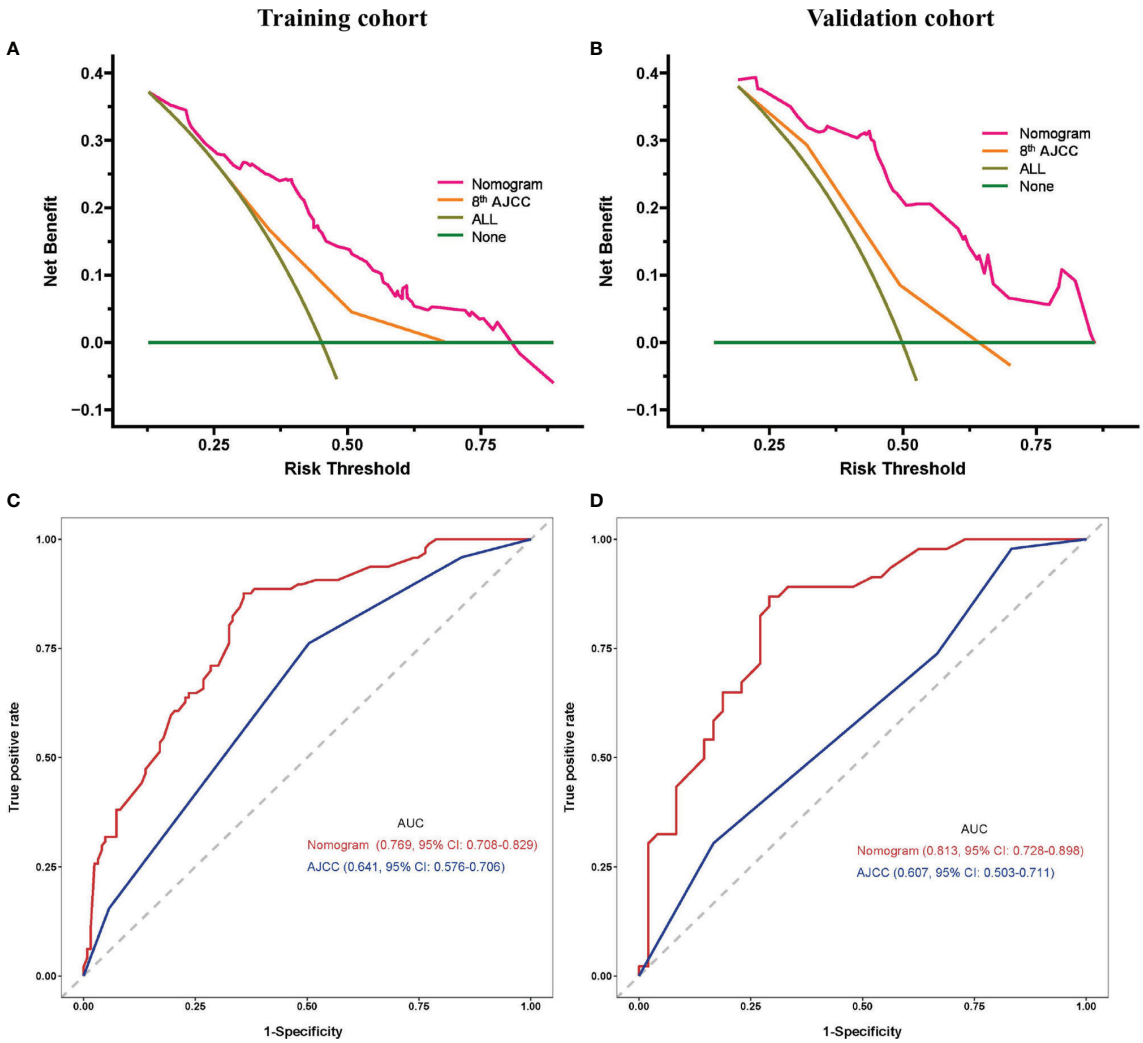

FIGURE 3 | Prognostic model comparisons. Decision curve analysis **(A, C)** and ROC curves **(B, D)** of the prognostic model and 8th AJCC stage for the training **(A, B)** and validation cohorts **(C, D)**. AJCC, American Joint Committee on Cancer; AUC, area under curve; CI, confidence interval.

metastasis, should routinely undergo lymphatic dissection. This is not only an essential step for radical treatment but also an important factor in clarifying the prognosis of patients. Tumor size was confirmed to be associated with the long-term survival of pCCA patients. DeOliveira et al. emphasized that patients with tumors larger than 3 cm have a poorer prognosis than those with smaller tumors (30). In addition, a larger tumor may indicate a poorer prognosis. For example, tumor size > 5 cm was revealed to be independently associated with poor long-term survival of pCCA (17). This may be because the location of pCCA is extremely special and often does not have a complete envelope. Therefore, as the size of the pCCA tumor continues to increase,

TABLE 4 | Comparison of the prognostic accuracies for 1-year RFS and OS of the nomogram and the 8th AJCC stage.

		Nomogram Training cohort	8th AJCC stage	*P*
RFS	C-index (95% CI)	0.723 (0.684-0.762)	0.641 (0.576-0.706)	< 0.001
OS	C-index (95% CI)	0.764 (0.727-0.801)	0.617 (0.580-0.654)	< 0.001
		Validation cohort		
RFS	C-index (95% CI)	0.743 (0.688-0.798)	0.607 (0.503-0.711)	< 0.001
OS	C-index (95% CI)	0.720 (0.663-0.777)	0.541 (0.470-0.612)	< 0.001

AJCC, American Joint Committee on Cancer; C-index, concordance index; OS, overall survival; RFS, recurrence-free survival.

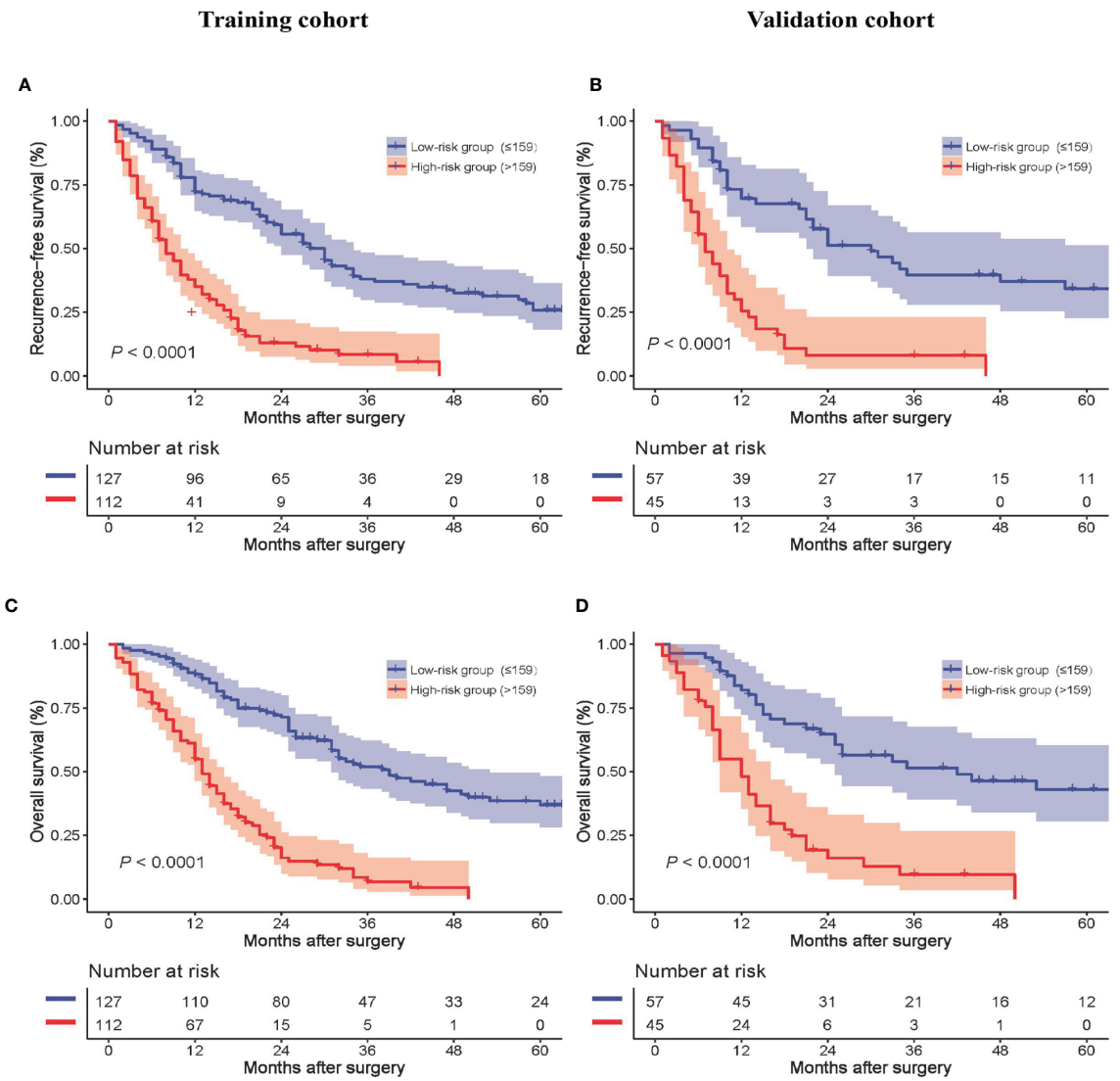

FIGURE 4 | Recurrence-free survival of all patients between the low- and high-risk groups in the training **(A)** and validation cohorts **(B)**. Overall survival of all patients between the low- and high-risk groups in the training **(C)** and validation cohorts **(D)**.

the probability of it invading the hepatic artery and portal vein may also increase. The scope of the tumor is increasing; at the cytological level, the possibility of early metastasis is increasing. Even if the margins are negative or the tumor is not visible to the eye, the possibility of complete elimination of tumor cells is reduced. Traditionally, it was believed that portal vein invasion had no effect on the long-term prognosis and could only determine the respectability of the tumor. However, recent research indicates that portal vein invasion was independently associated with worse OS than portal vein invasion (19). Although hepatic artery invasion commonly did not have an association with the resectability of pCCA, it had a significant effect on the poor prognosis of the patients. Branch or main hepatic artery invasion patients showed a poor OS compared to those without hepatic artery invasion due to the promotion of pCCA metastasis by hepatic artery invasion (35). Furthermore, we believe that, for pCCA, the tissue in which the tumor invades is related to the location of the tumor's initial growth and not directly related to the degree of malignancy of the tumor. Invasion of the hepatic artery or portal vein does not imply a difference in malignancy. As long as R0 resection can be achieved, the prognosis of patients will be prolonged. Therefore, we unified portal vein invasion and hepatic artery invasion as macrovascular invasion. CA19-9 has been widely used as a diagnostic or prognostic biomarker for several gastrointestinal cancers, including cholangiocarcinoma, gastric cancer, and colorectal cancer (36–38). pCCA patients with preoperative CA19-9 levels < 150 U/ml showed better long-term survival outcomes than those with higher CA19-9 levels (26). Moreover, a study found a negative association between

preoperative serum CA19-9 levels and the survival time of pCCA patients (19). However, the underlying mechanisms for the aberrant serum CA19-9 levels in pCCA patients are still unknown. In addition, tumor differentiation and microvascular invasion were both demonstrated to be independent predictive factors and to have a strong impact on the oncologic prognosis of resected pCCA (39–41).

The model can screen out high-risk recurrence patients (score > 159), guide decision-making for postoperative preventive adjuvant therapy, and help to decrease the incidence of recurrence, thereby prolonging the survival time of patients. At present, the role of adjuvant therapy in patients with resected pCCA is poorly defined, and there is a lack of data from phase III randomized controlled trials (42, 43). Therefore, we believe that for patients with a low risk of recurrence, follow-up should be strengthened initially instead of providing adjuvant therapy immediately. At the same time, we need to find the reasons for the low-risk recurrence of factors other than our model, such as whether these patients have already received postoperative chemotherapy. Several retrospective studies have suggested that adjuvant chemoradiation may improve long-term survival and local control, although distant metastases are still the most common mode of failure (44–47). Other researchers have suggested that adjuvant chemoradiation may have significant benefits only in patients with T3 or T4 tumors or those with a high risk of locoregional recurrence (positive margin or LN involvement) (46, 48, 49). In a systematic review and meta-analysis, Horgan et al. revealed an associated improvement in survival time (although nonsignificant) with adjuvant therapy compared with resection alone (50). Another systematic review and meta-analysis of 21 clinical trials indicated a significantly higher 5-year OS with postoperative adjuvant therapy in patients with extrahepatic cholangiocarcinoma (51). In addition, targeted therapy has made some progress in controlling recurrence. A phase III study including 185 patients with advanced *IDH1*-mutant cholangiocarcinoma caused significant improvement in progression-free survival (median 2.7 months *vs.* 1.4 months; HR: 0.37, $P < 0.001$) when treated with an *IDH1* inhibitor named ivosidenib compared to placebo (52). Therefore, we believe that patients with a high risk of recurrence should be screened out, and while follow-up is strengthened, postoperative adjuvant therapy should be recommended.

The first published prognostic model for pCCA is a risk score calculated with age, margin status, T stage, and adjuvant chemoradiation (53). This was flawed because it included only 96 patients and lacked data on important prognostic indicators, including lymph node status. Recently, Koerkamp et al. proposed a prognostic model for pCCA patients (18). In their model, three indicators, including LN status and count, differentiation, and margin status, were independent risk factors that affect disease-specific survival in patients with pCCA after surgery (18). Although the C-index of this model was 0.73, which showed a high predictive value for the oncologic prognosis of pCCA, our team thinks that it still has some limitations. For example, data from Asian populations are lacking, as well as serum tumor biomarkers such as CA19-9. Zhang et al. used the database from Surveillance, Epidemiology and End Results (SEER) to develop a more detailed tumor size model to predict the cancer-specific survival of pCCA, which was validated by Asian populations (20). However, the C-index of this model was only 0.626, and it also lacked serum tumor biomarkers, such as CA 19-9. Therefore, when our model was developed, our team specifically considered the importance of CA 19-9 to prognosis and added this parameter to our model. In addition, the data used to develop the abovementioned model were all from the SEER database or a single-center Western database because of the lack of data modeling in Eastern populations. In addition, none of the above models predict the recurrence of patients. Based on the multicenter Eastern database, we developed and validated an online prognostic model containing tumor biomarkers with excellent performance in predicting RFS.

This study has several limitations. First, this model lacked western external validation. We tried to use the SEER database for validation, but the SEER database lacked information on preoperative serum tumor biomarkers. Cooperating with other institutions for external validation is what we should continue to do. Second, 1 to 3 of the patients in this study had fewer than four LNs examined, and these patients were potentially understaged due to insufficient LN evaluation, which could rule out LN metastasis. Collecting at least four LNs has been essential. Previous research indicated that LN-negative patients had poorer long-term survival if fewer than four LNs were examined (14). However, although lymphadenectomy is a standard part of curative intent resection, most surgeries still have a high percentage of patients with fewer than four LNs examined. Thus, in our study, the LN status and count were all collected and added to the model to largely resolve the limitation. Third, only patients with R0 resection were included. Determining whether patients with R1 or R2 resection are suitable for this model requires more research. Fourth, this study lacked data for postoperative adjuvant therapy. The patients included in this study were recruited between 2008 and 2016. During this time, because there is a dearth of evidence from phase III RCTs, the usefulness of adjuvant chemotherapy or chemo-radiation therapy in patients with resected pCCA is unclear (42, 43). Therefore, we did not have a detailed record of data for postoperative adjuvant chemotherapy. However, more evidence proves that postoperative adjuvant chemotherapy may be beneficial for pCCA patients. We will perform more detailed records for adjuvant therapy in future studies.

CONCLUSION

Using a multicenter database, a prognostic model was developed and validated that can effectively predict 1-year RFS and screen out patients at high risk for recurrence (score > 159). Our research revealed that this model has significantly better predictive performance and clinical applicability than the 8th AJCC TNM staging system. The model is available as a simple and visual calculator *via* the web, making it more convenient for

clinicians to apply. Further prospective, large-scale, external validation in Western cohorts is warranted.

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 Southwest 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

Conception: H-SD, Z-YC. Study design: Z-PL, W-YC, LX, H-SD, Z-YC. Administrative support: H-SD, Z-YC. Data collection and acquisition: Z-PL, LX, YP, S-YZ, JB, YJ. Data analysis: Z-PL, W-YC, Z-RW, LX, Y-QZ, H-SD, Z-YC. Manuscript preparation: Z-PL, W-YC, Z-RW, YP, S-YZ, H-SD, Z-YC. Critical revision: Y-QZ, H-SD, Z-YC. Final approval of manuscript: All authors. Z-PL and W-YC contributed equally to this work. All authors contributed to the article and approved the submitted version.

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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.2022.849053/full#supplementary-material

Supplementary Figure 1 | Flow chart of patient inclusion. pCCA, perihilar cholangiocarcinoma.

Supplementary Table 1 | The corresponding score in our prediction model. ELN, examined lymph nodes; Carbohydrate antigen 19-9. Model score = Lymph node involvement + Maximum tumor size + Macrovascular invasion + Microvascular invasion + Tumor differentiation + CA 19-9.

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Prognostic Factors for 10-Year Survival in Patients With Hepatocellular Cancer Receiving Liver Transplantation

Quirino Lai[1], Andre Viveiros[2], Samuele Iesari[3], Alessandro Vitale[4], Gianluca Mennini[1], Simona Onali[5], Maria Hoppe-Lotichius[6], Marco Colasanti[7], Tommaso M. Manzia[8], Federico Mocchegiani[9], Gabriele Spoletini[10], Salvatore Agnes[10], Marco Vivarelli[9], Giuseppe Tisone[8], Giuseppe M. Ettorre[7], Jens Mittler[6], Emmanuel Tsochatzis[5], Massimo Rossi[1], Umberto Cillo[4], Benedikt Schaefer[2] and Jan P. Lerut[3], on behalf of the EurHeCaLT Study Group*

[1] General Surgery and Organ Transplantation Unit, Sapienza, Rome, Italy, [2] Department of Medicine I, Innsbruck University, Innsbruck, Austria, [3] Institut de Recherche Expérimental et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium, [4] Department of Surgical, Oncological and Gastroenterological Sciences, Padua University, Padua, Italy, [5] UCL Institute for Liver and Digestive Health and Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom, [6] Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Mainz University, Mainz, Germany, [7] Division of General Surgery and Liver Transplantation, San Camillo Hospital, Rome, Italy, [8] Department of Transplant Surgery, PTV University, Rome, Italy, [9] Unit of Hepatobiliary Surgery and Transplantation, Marche Polytechnic University, Ancona, Italy, [10] Catholic University - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

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Edited by:
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***Correspondence:**
Quirino Lai
quirino.lai@uniroma1.it

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Background: Long-term survival after liver transplantation (LT) for hepatocellular cancer (HCC) continues to increase along with the modification of inclusion criteria. This study aimed at identifying risk factors for 5- and 10-year overall and HCC-specific death after LT.

Methods: A total of 1,854 HCC transplant recipients from 10 European centers during the period 1987–2015 were analyzed. The population was divided in three eras, defined by landmark changes in HCC transplantability indications. Multivariable logistic regression analyses were used to evaluate the significance of independent risk factors for survival.

Results: Five- and 10-year overall survival (OS) rates were 68.1% and 54.4%, respectively. Two-hundred forty-two patients (13.1%) had HCC recurrence. Five- and 10-year recurrence rates were 16.2% and 20.3%. HCC-related deaths peaked at 2 years after LT (51.1% of all HCC-related deaths) and decreased to a high 30.8% in the interval of 6 to 10 years after LT. The risk factors for 10-year OS were macrovascular invasion (OR = 2.71; P = 0.001), poor grading (OR = 1.56; P = 0.001), HCV status (OR = 1.39; P = 0.001), diameter of the target lesion (OR = 1.09; P = 0.001), AFP slope (OR = 1.63; P = 0.006), and patient age (OR = 0.99; P = 0.01). The risk factor for 10-year HCC-related death were AFP slope (OR = 4.95; P < 0.0001), microvascular (OR = 2.13; P < 0.0001) and macrovascular invasion (OR = 2.32; P = 0.01), poor tumor grading (OR = 1.95; P = 0.001), total number of neo-adjuvant therapies (OR = 1.11; P = 0.001), diameter of the target lesion (OR = 1.11; P = 0.002), and patient age (OR = 0.97; P = 0.001). When analyzing survival rates in function of LT era, a progressive improvement of the results was observed, with patients transplanted during the period 2007–2015 showing 5- and 10-year death rates of 26.8% and 38.9% (vs. 1987–1996, P < 0.0001; vs. 1997–2006, P = 0.005).

Conclusions: LT generates long-term overall and disease-free survival rates superior to all other oncologic treatments of HCC. The role of LT in the modern treatment of HCC becomes even more valued when the follow-up period reaches at least 10 years. The results of LT continue to improve even when prudently widening the inclusion criteria for transplantation. Despite the incidence of HCC recurrence is highest during the first 5 years post-transplant, one-third of them occur later, indicating the importance of a life-long follow-up of these patients.

Keywords: recurrence, alpha-fetoprotein, radiological response, Milan criteria, expanded criteria

INTRODUCTION

Liver transplantation (LT) represents the gold-standard therapy to cure well-selected patients with hepatocellular cancer (HCC) (1). Before 1996, the absence of internationally recognized inclusion criteria explained the poor results of LT in patients with HCC (2). The introduction of the Milan criteria in clinical practice strongly modified the outcomes, resulting in 5-year survival rates similar to those obtained in non-HCC patients (3, 4). However, the rigorous adoption of these criteria significantly limits access to potentially successful treatment to a large number of patients, even slightly exceeding the selection criteria. Therefore, the transplant community widened in recent years the selection criteria for LT, thereby increasing the number of transplanted without impairing the expected results (5–7). Reporting of outcome is usually limited to 5-year survival rates. The impact of LT in the very long follow-up (i.e., ≥10 years) is still an unanswered question, especially when compared to other (curative) approaches such as liver resection (8).

In this light, it was hypothesized that LT should provide a beneficial 10-year survival impact. The study aimed at exploring the risk factors for 5- and 10-year death and HCC-specific death in a large international population of HCC liver patients.

METHODS

Study Design

This is a retrospective international study carried out on prospectively maintained databases identifying adult (≥18 years) patients enlisted and transplanted with the primary diagnosis of HCC. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (9). The institutional review board of Azienda Ospedaliero-Universitaria Policlinico Umberto I (coordinating center) approved the study.

Setting

Participants included 10 centers composing the EurHeCaLT Study Group. The centers participating in the study were as follows: Innsbruck University, Innsbruck, Austria (n = 296); Université Catholique de Louvain, Brussels, Belgium (n = 283); Padua University, Padua, Italy (n = 267); Sapienza University of Rome, Rome, Italy (n = 195); Royal Free Hospital, London, UK (n = 193); Mainz University, Mainz, Germany (n = 176); San Camillo Hospital, Rome, Italy (n = 142); PTV University Rome, Rome, Italy (n = 122); University of Marche, Ancona, Italy (n = 95); and Catholic University Rome, Rome, Italy (n = 85).

Population

The investigated population included consecutive adult (≥18 years) patients enlisted and transplanted with the primary diagnosis of HCC during the period 1987–2015. Patients with HCC diagnosed only at pathological examination (incidental HCC), mixed hepatocellular-cholangiocellular cancer, and cholangiocellular cancer misdiagnosed as HCC were not included in the study.

Variables and Data Collection

Collected patient-related data included the following: age and sex, cause of cirrhosis [hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol, non-alcoholic steato-hepatitis (NASH), and other diseases], waiting time (WT) duration, model for end-stage liver disease (MELD), and period of LT (1987–1996, 1997–2006, and 2007–2015). Pre-LT available tumor-related data were morphologic HCC characteristics and alpha-fetoprotein (AFP) values evaluated at first referral and last pre-LT assessment, neo-adjuvant treatment(s), and subsequent modified Response Evaluation Criteria in Solid Tumors (mRECIST) status.

Tumor-related data obtained at pathological specimens were morphologic characteristics, multi-focality, bi-lobarity, poor grading, and micro- and macrovascular invasion. In all cases, morphologic HCC aspects referred to vital tumor tissue only.

Definitions

Patient death was defined as any death caused by tumor- and non-tumor–related causes observed during the entire post-transplant follow-up. Patient death time was calculated as the time from LT to death after LT during the follow-up.

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; ELTR, European Liver Transplant Registry; HBV, hepatitis B virus; HCC, hepatocellular cancer; HCV, hepatitis C virus; IQR, interquartile range; LRT, loco-regional therapy; LT, liver transplantation; MELD, model for end-stage liver disease; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NASH, non-alcoholic steato-hepatitis; OR, odds ratio; OS, overall survival; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TACE, trans-arterial chemo-embolization; WT, waiting time.

HCC-specific death was defined as a death directly caused by a tumor recurrence observed during the follow-up.

HCC recurrence was defined as any hepatic and/or extra-hepatic reappearance of the tumor at any time from the LT. Tumor recurrence time was calculated as the time from LT to detect tumor recurrence after LT during the follow-up. The last follow-up date was December 31, 2021.

The periods of LT were defined according to the introduction of some innovation in the field of transplant oncology: period 1987–1996 corresponding to the pre-Milan criteria era (liberal approach); (2) period 1997–2006 to the Milan criteria era; (3,4) and period 2007–2015 corresponding to the expanded criteria era (safe enlargement of inclusion criteria). In detail, the Up-to-seven criteria or the UCSF criteria were adopted in the different centers, with the exception of the Padua center, adopting the HCC-MELD score based on benefit principles (5–7).

Statistical Analysis

Baseline characteristics of each data set were presented as medians and interquartile ranges (IQRs) for continuous variables and as numbers and percentages for discrete variables. Kruskal–Wallis test was adopted for comparing continuous variables. Chi-squared test was adopted for comparing dichotomous variables. Data missingness is detailed in **Supplementary Table 1**. In all the cases, covariates included in the analysis had missing data <10%. Missed data were handled with a single imputation method, and a median of nearby points was adopted (10).

Multivariable logistic regression analyses were used to evaluate the significance of independent risk factors for survival as independent prognostic factors for observed 5- and 10-year overall survival (OS) and for HCC-specific 5- and 10-year survival. The investigated variables were initially introduced using a "full model" approach, and then, the most relevant ones were selected using a backward Wald method with the intent to develop more parsimonious models. Odds ratios (ORs) and 95.0% confidence intervals (95.0% CIs) were reported.

Kaplan–Meier survival estimates were used to calculate survival curves. Log-rank test was used for comparing the survival distributions of different groups. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 27.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics are reported in **Table 1**. A total of 1,854 patients were enrolled for the present study. The median follow-up was 46.4 months (IQR: 16.4–90.0). A total of 751 (40.5%) and 256 (13.8%) patients overpassed the 5 and 10 years of follow-up, respectively.

The median age of the patients was 57 years (IQR = 49–62), males (n = 1,564, 84.4%) largely outnumbered female patients. The main underlying liver disease was HCV, followed by alcoholic-related cirrhosis. The median MELD value was 12 (IQR = 9–15). The median duration of the waiting time was 4 months (IQR = 2–9).

Median diameter of the target lesion at time of LT was 2.0 cm, with a higher prevalence of single lesions. The median pre-LT

TABLE 1 | Patient demographic data and tumor features at first referral, last radiological assessment before LT, and pathological examination.

Variables	Median (IQR) or n (%)
Sex M/F	1,564/290 (84.4/15.6)
Age, years	57 (49–62)
Period of LT	
1987–1996	106 (5.7)
1997–2006	615 (33.2)
2007–2015	1,133 (61.1)
Waiting time, months	4 (2–9)
Underlying liver pathology*	
HCV	889 (48.0)
HBV	344 (18.6)
Alcohol	547 (29.5)
NASH	105 (5.7)
Other	132 (7.1)
MELD	12 (9–15)
Diameter of the target lesion, cm	
At first referral	2.5 (2.0–3.8)
Before LT	2.0 (1.0–3.0)
Number of nodules	
At first referral	1 (1–3)
Before LT	1 (1–3)
Milan criteria-out status	
At first referral	574 (31.0)
Before LT	404 (21.8)
AFP, ng/mL	
At first referral	10 (5–39)
Before LT	10 (5–33)
AFP slope ≥15 ng/ml/month	170 (9.2)
Type of response mRECIST after LRT	
Complete response	337 (18.2)
Partial response	535 (28.9)
Stable disease	219 (11.8)
Progressive disease	299 (16.1)
No LRT/no pre-LT evaluation after last LRT	464 (25.0)
Pre-LT LRT	1,524 (82.2)
Type of LRT**	
TACE	1,190 (64.2)
RFTA	367 (19.8)
PEI	321 (17.3)
Hepatic resection	173 (9.3)
TARE	26 (1.4)
SBRT	3 (0.2)
Pathological tumor features	
Diameter of the target lesion, cm	2.4 (1.5–3.5)
Number of nodules	2 (1–3)
Multifocality	976 (52.6)
Bilobar tumor	469 (25.3)
Poor grading	328 (17.7)
Microvascular invasion	394 (21.3)
Macrovascular invasion	56 (3.0)

** In some cases, same patients presented multiple pathologies. ** In some cases, same patients received multiple approaches.*

IQR, interquartile ranges; n, number; M, male; F, female; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; mRECIST, modified Response Evaluation Criteria In Solid Tumors; LRT, loco-regional therapy; TACE, trans-arterial chemo-embolization; RFTA, radio-frequency termo-ablation; PEI, percutaneous ethanol injection; TARE, trans-arterial radio-embolization; SBRT, stereotactic body radiation therapy.

TABLE 2 | Different survivals rates in the analyzed population.

Survival rates (%)	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Overall survival	85.6	79.9	75.3	72.0	68.1	66.0	63.2	59.5	57.5	54.4
HCC-related death	1.9	5.3	7.9	9.7	11.4	12.8	14.0	15.9	16.1	16.7
Non-HCC–related death	12.7	15.6	18.3	20.3	23.1	24.3	26.5	29.3	31.4	34.7
HCC recurrence	4.8	9.2	12.0	14.4	16.2	18.0	18.7	20.0	20.3	20.3

HCC, hepatocellular cancer.

AFP value was 10 ng/ml; 170 (9.2%) patients presented an AFP-slope >15 ng/ml/month during the waiting time. Neo-adjuvant treatment was applied in 82.2% of cases. Trans-arterial chemo-embolization (TACE) was the most commonly adopted loco-regional therapy (LRT), followed by radio-frequency ablation. Salvage LT after resection was carried out in 173 (9.3%) cases. A complete radiological tumor response was obtained in 337 (18.2%) of patients, and 299 (16.1%) patients had a progressive disease.

At pathological examination of the hepatectomy specimen, the median diameter of the target lesion was 2.4 cm, and the median number of lesions was 2. A poor tumor grading was observed in 328 (17.7%) cases. Micro- and macrovascular invasions were present in 394 (21.3%) and 56 (3.0%) patients, respectively.

Patient Survival, HCC-Related Death, and Recurrence Estimates

During the follow-up period, 651 of 1,854 (35.1%) liver patients died: 512 (27.6%) patients died within the first 5 years post-LT, 104 (5.6%) between 6 and 10 years, and 35 (1.9%) more than 10 years after LT. In **Table 2**, different measures of survival were reported. The 5- and 10-year Kaplan–Meier OS estimates were 68.1% and 54.4%, respectively (**Figure 1**).

A total of 180 (9.7%) and 471 (25.4%) deaths were HCC-related and no HCC-related, respectively. Five- and 10-year HCC-related and non-HCC–related death estimates were 11.4% and 16.7% vs. 23.1% and 37.4%, respectively (**Figure 1**).

In relation to the timeline of post-LT deaths, a fast increase of the tumor-related deaths was seen with a peak during the second post-LT year (51.1% of death causes). Later on, a slight decline was observed (third year = 46.4%; fourth year = 43.2; fifth year = 35.6%). The percentage of cancer-related deaths between 6 and 10 years post-LT was surprisingly high (30.8%). The risk of dying from an HCC-related cause lowered to 9.1% and 8.3%, respectively, during the post-LT periods of 11–15 and >15 years (**Figure 2**).

Two hundred forty-two (13.1%) recurrences were reported; 62 (3.4%) of these patients were still alive at the last follow-up. The 5- and 10-year Kaplan–Meier recurrence rates were 16.2% and 20.3%.

Risk Factors for Overall Patient Death

Two separate multivariable logistic regression analyses were performed to explore the features connected with increased odds for the risk of 5- and 10-year death for any cause (**Table 3**). Observing the independent risk factors for 5-year death, macrovascular invasion showed the highest OR of 3.60

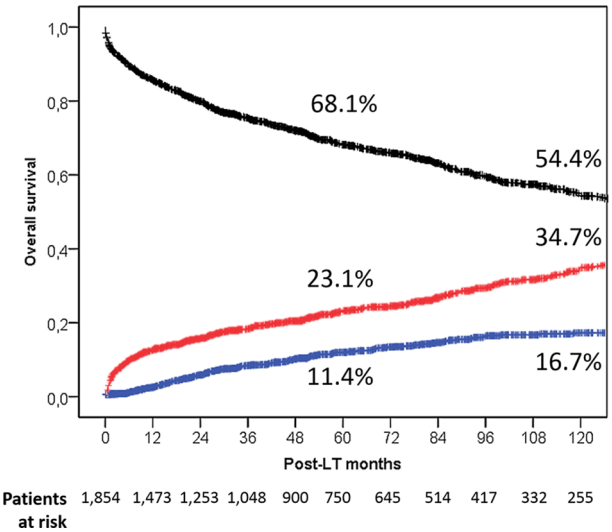

FIGURE 1 | Overall patient survival rates in the entire population (black line). Death rates caused by tumor (blue line) and caused by other causes (red line) are also reported.

(P < 0.0001), followed by the diameter of the target lesion (OR = 1.12; P < 0.0001), poor grading (OR = 1.40; P = 0.01), AFP slope > 15 ng/ml/month (OR = 1.52; P = 0.02), and MELD score (OR = 1.02; P = 0.02).

Recalculating the odds with a time horizon of 10 years, the following variables confirmed their negative prognostic impact: macrovascular invasion (OR = 2.71; P = 0.001), diameter of the target lesion (OR = 1.09; P = 0.001), poor grading (OR = 1.56; P = 0.001), and AFP slope (OR = 1.63; P = 0.006). In contrast, MELD score lost its relevance. HCV status (OR = 1.39; P = 0.001) and patient age (OR = 0.99; P = 0.01) reported statistically relevant odds in this long-term analysis.

Risk Factors for HCCRelated Death

Two separate multivariable logistic regression analyses were utilized to explore the features connected with increased odds for the risk of 5- and 10-year HCC-related death (**Table 4**).

Again, similar variables were observable in the two models. As for the risk of 5-year HCC-specific death, AFP slope had the highest OR of 4.50 (P < 0.0001), followed by microvascular invasion (OR = 2.02; P = 0.001), macrovascular invasion (OR = 2.82; P = 0.003), diameter of the target lesion (OR = 1.11; P = 0.004), poor grading (OR = 1.80; P = 0.007), and number of nodules (OR = 1.07; P = 0.009). Patient age (OR = 0.97; P =

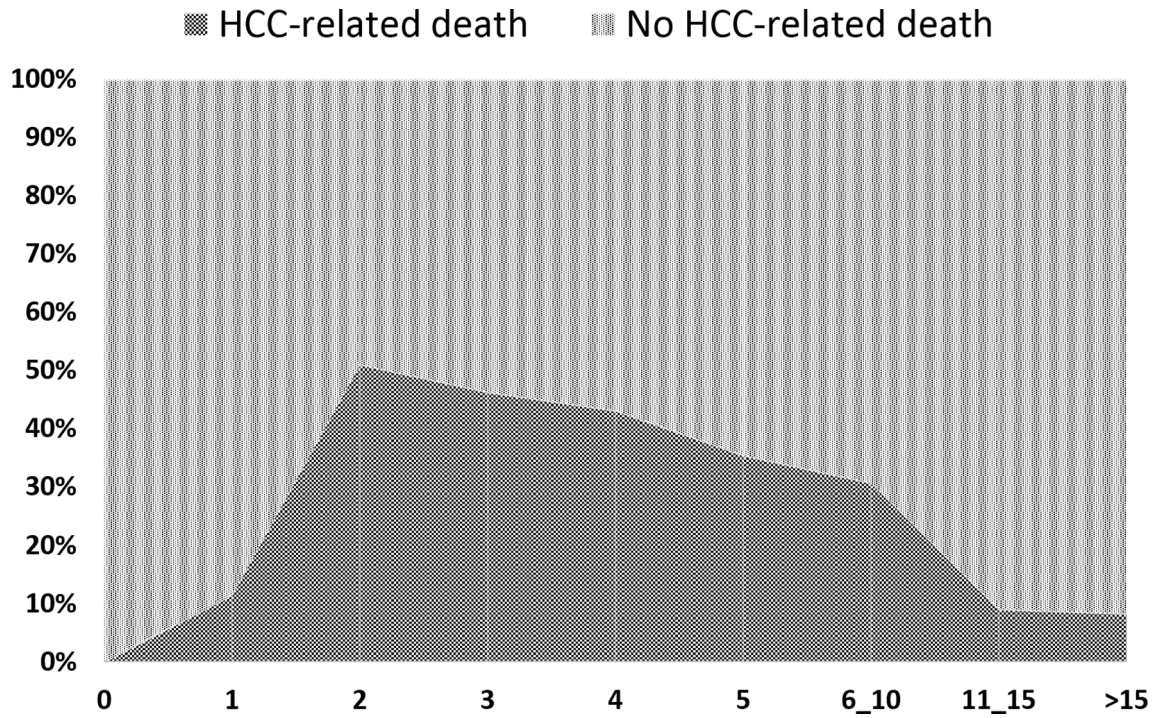

FIGURE 2 | Causes of death expressed in percentages on the total number of cases at different time point of the follow-up.

TABLE 3 | Multivariable logistic regression analysis for the risk of 5- and 10-year death after LT (backward Wald method).

Variables	Beta	SE	Wald	OR	95.0% CI		P-value
					Lower	Upper	
5-year death*							
Macrovascular invasion	1.28	0.31	17.25	3.60	1.97	6.58	<0.0001
Diameter target lesion cm	0.11	0.03	16.60	1.12	1.06	1.18	<0.0001
Poor grading (G3-4)	0.34	0.14	6.26	1.40	1.08	1.83	0.01
AFP slope >15 ng/ml/month	0.42	0.18	5.42	1.52	1.07	2.17	0.02
MELD	0.02	0.01	5.17	1.02	1.00	1.04	0.02
Constant	–1.71	0.16	112.60	0.18	–	–	<0.0001
10-year death**							
Poor grading (G3-4)	0.45	0.13	11.80	1.56	1.21	2.02	0.001
Diameter target lesion cm	0.09	0.03	11.28	1.09	1.04	1.14	0.001
Macrovascular invasion	0.997	0.31	10.38	2.71	1.48	4.97	0.001
HCV	0.33	0.10	10.28	1.39	1.14	1.69	0.001
AFP slope >15 ng/ml/month	0.49	0.18	7.68	1.63	1.15	2.30	0.006
Patient age	–0.01	0.01	5.98	0.99	0.98	0.997	0.01
Constant	–0.52	0.32	2.71	0.59	–	–	0.100

*Hosmer–Lameshow test: *0.76; **0.49.*

Variables initially tested in the model: patient age, sex, waiting list duration, HCV, HBV, alcohol, NASH, MELD, Milan criteria out at transplant, mRECIST complete response, mRECIST progressive disease, AFP value at transplant, AFP slope >15 ng/ml/month, diameter target lesion cm, number of nodules, multifocality, bilobarity, poor grading (G3-4), microvascular invasion, macrovascular invasion, pre-LT LRT, total number of LRT, salvage transplant after resection.

SE, standard error; OR, odds ratio; CI, confidence intervals; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; mRECIST, modified Response Evaluation Criteria In Solid Tumors; LT, liver transplantation; LRT, loco-regional therapy.

0.002) and MELD score (OR = 0.95; P = 0.04) were protective for the risk of HCC-specific death.

When the time horizon was set at to 10 years, the relevant role of AFP slope was confirmed (OR = 4.95; P < 0.0001), followed by microvascular (OR = 2.13; P < 0.0001) and macrovascular invasion (OR = 2.32; P = 0.01), poor tumor grading (OR = 1.95; P = 0.001), total number of neo-adjuvant therapies (OR = 1.11; P = 0.001), and diameter of the target lesion (OR = 1.11; P = 0.002). Again, patient age was a protective factor (OR = 0.97; P = 0.001).

TABLE 4 | Multivariable logistic regression analysis for the risk of 5- and 10-year HCC-related death after LT (backward Wald method).

Variables	Beta	SE	Wald	OR	95.0% CI		P-value
					Lower	Upper	
5-year HCC-related death*							
AFP slope >15 ng/ml/month	1.50	0.22	45.15	4.50	2.90	6.98	<0.0001
Microvascular invasion	0.71	0.22	10.60	2.02	1.32	3.10	0.001
Patient age	–0.03	0.01	9.73	0.97	0.95	0.99	0.002
Macrovascular invasion	1.04	0.35	8.96	2.82	1.43	5.57	0.003
Diameter target lesion cm	0.11	0.04	8.27	1.11	1.03	1.19	0.004
Poor grading (G3-4)	0.59	0.22	7.40	1.80	1.18	2.75	0.007
Number of nodules	0.06	0.02	6.81	1.07	1.02	1.12	0.009
MELD score	–0.05	0.02	4.43	0.95	0.91	0.997	0.04
Constant	–1.47	0.63	5.46	0.23	–	–	0.02
10-year HCC-related death**							
AFP slope >15 ng/ml/month	1.60	0.21	56.95	4.95	3.27	7.49	<0.0001
Microvascular invasion	0.76	0.20	14.88	2.13	1.45	3.12	<0.0001
Poor grading (G3-4)	0.67	0.20	11.39	1.95	1.32	2.88	0.001
Patient age	–0.03	0.009	10.93	0.97	0.95	0.99	0.001
Total number of LRT	0.10	0.03	10.19	1.11	1.04	1.18	0.001
Diameter target lesion cm	0.11	0.04	9.48	1.11	1.04	1.19	0.002
Macrovascular invasion	0.84	0.34	6.14	2.32	1.19	4.52	0.01
Constant	–1.98	0.52	14.67	0.14	–	–	<0.0001

*Hosmer–Lameshow test: *0.13; **0.39.*

Variables initially tested in the model: patient age, sex, waiting list duration, HCV, HBV, alcohol, NASH, MELD, Milan criteria out at transplant, mRECIST complete response, mRECIST progressive disease, AFP value at transplant, AFP slope >15 ng/ml/month, diameter target lesion cm, number of nodules, multifocality, bilobarity, poor grading (G3-4), microvascular invasion, macrovascular invasion, pre-LT LRT, total number of LRT, salvage transplant after resection.

SE, standard error; OR, odds ratio; CI, confidence intervals; HCC, hepatocellular cancer; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; LRT, loco-regional therapy; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; mRECIST, modified Response Evaluation Criteria In Solid Tumors; LT, liver transplantation.

Correlation Between Death and Period of Transplant

Relevant differences existed among the different periods in terms of patient and tumor characteristics and clinical management, as reported in **Table 5**. In light of these aspects, a sub-analysis was done focused on the different risk factors for 10-year HCC-related death in the three different periods (**Table 6**). In detail, the slope of AFP was always the most relevant risk factors in all the different periods. The number of LRT emerged as a detrimental factor only in the last two periods, in which the pre-LT management with multiple LRT has raised as a routine approach in HCC transplant candidates.

When analyzing survival rates in function of LT era, a progressive improvement of the results was observed (**Figure 3**). Patients transplanted during the 1987–1996 "liberal era", characterized by the absence of any recognized inclusion criterion, had exceedingly high 5- and 10-year overall death rates of 59.4% and 68.0%. As expected, the results improved significantly during the 1997–2006 "Milan criteria era", with 5- and 10-year death rates declining to of 33.8% and 47.7%. Log-rank test showed a statistically relevant difference between these two eras ($P < 0.0001$). Last, the results further improved during the 2007–2015 "safe criteria enlargement era", with 5- and 10-year death rates of 26.8% and 38.9%. During this latter period, Milan criteria were progressively expanded by introducing San Francisco and Up-to-seven criteria. Interestingly, log-rank analysis survival rates were significantly improved when compared to those obtained during the first ($P < 0.0001$) and second era ($P = 0.005$).

Five- and 10-year HCC-related death rates were 35.6% and 41.7%, 12.6% and 18.0%, and 8.0% and 11.3% during the periods 1987–1996, 1997–2006, and 2007–2015, respectively. It was interesting to note that the latter period showed better results despite a slight enlargement of the criteria was adopted during this period respect to the previous one ($P = 0.005$).

DISCUSSION

In the present study, the 5- and 10-year survival rates of 68.1% and 54.4% observed in a large European cohort containing 1,854 patients with HCC compared favorably with the widely accepted lower limit for 5-year patient survival after LT of 50% (11).. These results are in line with findings reported in large international databases such as the European Liver Transplant Registry (ELTR), which reported, in a cohort of 18,349 HCC liver patients, 5- and 10-year survival rates of 66% and 51%, respectively (12).

Compared to all other therapeutic modalities, the long-term superiority of LT does not disserve sufficient attention within the medical community, although well known since long time (13).

A recent Chinese study including 1,255 patients with HCC compared the 10-year survival outcomes from three different first-line treatments, namely, radiofrequency ablation, liver resection, and transplantation. LT was clearly superior in terms of 10-year survival, even after adjustment for confounders and balancing of the compared cohorts using inverse probability weighting (8). A meta-analysis comparing LT and resection as

TABLE 5 | Patient demographic data and tumor features at first referral and last radiological assessment before LT in the three different periods.

Variables	1987–1996 (n = 106, 5.7%)	1997–2006 (n = 615, 33.2%) Median (IQR) or n (%)	2007–2015 (n= 1,133, 61.1%)	P-value
Sex M/F	84/22 (79.2/20.8)	517/98 (84.1/15.9)	963/170 (85.0/15.0)	0.29
Age, years	51 (41–58)	55 (40–61)	58 (52–63)	<0.0001
Waiting time, months	1 (0–3)	5 (2–10)	4 (2–9)	<0.0001
Underlying liver pathology*				
HCV	45 (42.5)	295 (48.0)	549 (48.5)	0.50
HBV	31 (29.2)	121 (19.7)	192 (16.9)	0.005
Alcohol	15 (14.2)	167 (27.2)	365 (32.3)	<0.0001
NASH	1 (0.9)	30 (4.9)	74 (6.5)	0.04
Other	22 (20.8)	34 (5.5)	76 (6.7)	<0.0001
MELD	12 (12–12)	12 (10–15)	12 (9–15)	0.03
Diameter of the target lesion, cm				
At first referral	3.0 (2.5–5.0)	2.5 (2.0–3.7)	2.5 (1.9–3.7)	<0.0001
Before LT	1 (1–3)	1 (1–2)	1 (1–3)	0.08
Number of nodules				
At first referral	3.0 (2.0–5.2)	2.0 (1.2–3.0)	1.8 (0.8–2.8)	<0.0001
Before LT	1 (1–3)	1 (1–3)	1 (1–3)	0.13
Milan criteria-out status				
At first referral	46 (43.4)	175 (28.5)	353 (31.2)	0.009
Before LT	48 (45.3)	114 (18.5)	242 (21.4)	<0.0001
AFP, ng/mL				
At first referral	13 (6–195)	13 (5–52)	10 (5–30)	<0.0001
Before LT	31 (88–385)	10 (5–41)	8 (4–24)	<0.0001
AFP slope ≥15 ng/ml/month	37 (34.9)	45 (7.3)	88 (7.8)	<0.0001
Type of response mRECIST after LRT				
Complete response	1 (0.9)	99 (16.1)	237 (20.9)	<0.0001
Partial response	17 (16.0)	180 (29.3)	338 (29.8)	0.01
Stable disease	4 (3.8)	103 (16.7)	112 (9.9)	<0.0001
Progressive disease	6 (5.7)	72 (11.7)	221 (19.5)	<0.0001
No LRT/no pre-LT evaluation after last LRT	79 (74.5)	161 (26.2)	224 (19.8)	<0.0001
Pre-LT LRT	33 (31.1)	511 (83.1)	980 (86.5)	<0.0001
Type of LRT**				
TACE	23 (21.7)	408 (66.3)	759 (67.0)	<0.0001
RFTA	0 (-)	61 (9.9)	306 (27.0)	<0.0001
PEI	8 (7.5)	116 (18.9)	197 (17.4)	0.02
Hepatic resection	4 (3.8)	46 (7.5)	123 (10.9)	0.009
TARE	0 (-)	0 (-)	26 (2.3)	<0.0001
SBRT	0 (-)	0 (-)	0 (-)	0.38

** In some cases, same patients presented multiple pathologies. ** In some cases, same patients received multiple approaches.*
IQR, interquartile ranges; n, number; M, male; F, female; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; mRECIST, modified Response Evaluation Criteria In Solid Tumors; LRT, loco-regional therapy; TACE, trans-arterial chemo-embolization; RFTA, radio-frequency termo-ablation; PEI, percutaneous ethanol injection; TARE, trans-arterial radio-embolization; SBRT, stereotactic body radiation therapy.

the treatment options in small HCC meeting the Milan criteria reported that the 5-year OS rates were similar, whereas the 10-year rates were significantly higher in patients who underwent LT than resection (50.0 vs. 29.8%; P < 0.001) (14).

These findings were also confirmed when the concept of "transplant benefit" was investigated. Exploring the data of 1,028 HCC cirrhotic patients coming from one Eastern and two Western surgical units, the 10-year scenario increased drastically the transplant benefit in all subgroups of resectable patients, and LT became an effective therapy for all patients without microvascular invasion independent of tumor extension and for oligo-nodular HCC with microvascular invasion meeting the conventional Milan and San Francisco criteria (15).

The present study confirms that a combination of morphological and biological tumor variables is linked to risk of death and HCC recurrence. A large US experience including 3,276 patients validated the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score, consisting of AFP value at LT, microvascular invasion, and the sum of the largest viable tumor and number of tumors in the total hepatectomy specimen (16). Interestingly, all these variables were statistically relevant risk factors for 10-year HCC-related death in our series.

Moreover, we explored the AFP dynamics during the waiting time instead of looking at the last available value before LT. Several studies assigned a relevant role to the AFP slope as a predictor for recurrence and death (17–19).

Macrovascular invasion is another relevant variable that has been recently explored in large international series. A retrospective study analyzing 45 patients with macrovascular patients before LT reported a very high risk of recurrence especially if the AFP value at LT was >10 ng/ml (5-year disease-free survival rates 27.8 vs. 71.8%; P = 0.008) (20). A ELTR study (n = 9,324) reported that vascular invasion overruled as prognostic indicator all criteria

TABLE 6 | Multivariable logistic regression analysis for the risk of 10-year HCC-related death after LT (backward Wald method) in the three different periods.

Variables	Beta	SE	Wald	OR	95.0% CI		P-value
					Lower	Upper	
1987–1996*							
AFP slope >15 ng/ml/month	3.84	0.85	20.66	46.64	8.90	244.54	<0.0001
Microvascular invasion	1.58	0.58	7.33	4.83	1.54	15.13	0.007
Milan criteria out	–1.63	0.85	3.67	0.20	.04	1.04	0.055
Constant	–2.50	0.51	23.87	0.08	–	–	<0.0001
1997–2006**							
AFP slope >15 ng/mlmonth	1.62	0.36	20.11	5.07	2.50	10.32	<0.0001
Poor grading	1.18	0.29	16.38	3.26	1.84	5.77	<0.0001
Number of nodules	0.12	0.05	6.73	1.13	1.03	1.24	0.009
Total number of LRT	0.13	0.05	6.27	1.14	1.03	1.25	0.01
Microvascular invasion	0.58	0.30	3.88	1.79	1.00	3.18	0.049
Constant	–3.10	0.25	155.56	0.05	–	–	<0.0001
2007–2015***							
AFP slope >15 ng/ml/month	1.26	0.35	13.30	3.54	1.79	6.97	<0.0001
HBV	1.25	0.39	10.43	3.50	1.64	7.50	0.001
Diameter target lesion	0.16	0.05	9.13	1.18	1.06	1.31	0.003
Microvascular invasion	0.84	0.31	7.61	2.33	1.28	4.24	0.006
Macrovascular invasion	1.35	0.53	6.62	3.87	1.38	10.86	0.01
Total number of LRT	0.12	0.05	4.84	1.12	1.01	1.24	0.03
Milan criteria out	0.70	0.32	4.72	2.01	1.07	3.78	0.03
HCV	0.69	0.35	3.99	2.00	1.01	3.93	0.046
Constant	–5.18	0.43	146.36	0.01	–	–	<0.0001

*Hosmer–Lameshow test: *0.78; **0.32; ***0.16.*

Variables initially tested in the model: patient age, sex, waiting list duration, HCV, HBV, alcohol, NASH, MELD, Milan criteria out at transplant, mRECIST complete response, mRECIST progressive disease, AFP value at transplant, AFP slope >15 ng/ml/month, diameter target lesion cm, number of nodules, multifocality, bilobarity, poor grading (G3-4), microvascular invasion, macrovascular invasion, pre-LT LRT, total number of LRT, salvage transplant after resection.

SE, standard error; OR, odds ratio; CI, confidence intervals; HCC, hepatocellular cancer; AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; LRT, loco-regional therapy; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; mRECIST, modified Response Evaluation Criteria In Solid Tumors; LT, liver transplantation.

based on size and number of nodules; 5-year OS rates reached 39.6%, 58.8%, and 73.2% in patients with macrovascular invasion, microvascular invasion, or absent invasion (21). All these experiences are in line with our findings. Both micro- and macrovascular invasion at pathological examination of the hepatectomy specimen correlated with poor tumor-related survival. The growing role of advanced locoregional therapies like the radio-embolization is showing promising results in terms of efficacious downstaging of macrovascular invasion using "superdownstaging" protocols (22).

In relation to the total number of neo-adjuvant treatments, several studies explored the negative effect of repeated therapies as a surrogate of a more aggressive tumor behavior. A large US experience including 789 Milan criteria-out HCC patients reported a detrimental effect of LRT in patients failing to be successfully downstaged when compared to directly transplanted patients (HCC recurrence: 34.1% vs. 26.1%; $p < 0.001$) (23). A European experience based on the analysis of 1,083 Milan criteria-in patients reported that up to three LRTs are beneficial for success in intention-to-treat LT patients, but, if patients need more LRT, this benefit is lost (24). Our series confirmed that the risk for long-term tumor-related death was increased in patients requiring more LRT, supporting the hypothesis that the need for more LRT is equivalent to higher tumor aggressiveness.

Our study explored the impact of risk factors available at the time of LT only, whereas other relevant aspects such as the role of immunosuppressive treatment were not. Despite there is some recent evidence that immunosuppression either as maintenance or anti-rejection treatment may play a role as another risk factor for HCC recurrence after transplantation, it was not explored because intending to investigate only variables that are available at the time of LT (25, 26). The investigation of variables obtainable after LT in fact introduces an "immortal bias" into the analysis. This potential risk was avoided excluding all the post-LT variables.

Our analysis confirmed the negative role of HCV infection on the long-term survival. During the studied time period, early viral allograft reinfection was universal. Nowadays, direct-acting antiviral agents have almost eliminated this risk for death. Therefore, it has to be foreseen that HCV infection will lose its role as a relevant risk factor for long-term death (27).

In the future, the prevalence of NASH will become the main reason to LT in patients with HCC, and this underlying disease will replace very soon HCV as a risk factor for delayed death after LT (28). In our series, the impact of NASH appears to be relatively limited, but its raising role is clearly reported observing the growing number of cases observed in the different LT periods.

Interestingly, in our series many patients (71 of 242; 29.3%) recurred very late (>5 years). Unfortunately, it was impossible to analyze more in detail if these recurrences were "real" ones or *de novo* HCCs in the transplanted graft (29, 30). The very late detection of HCC in this series suggests that one should be very

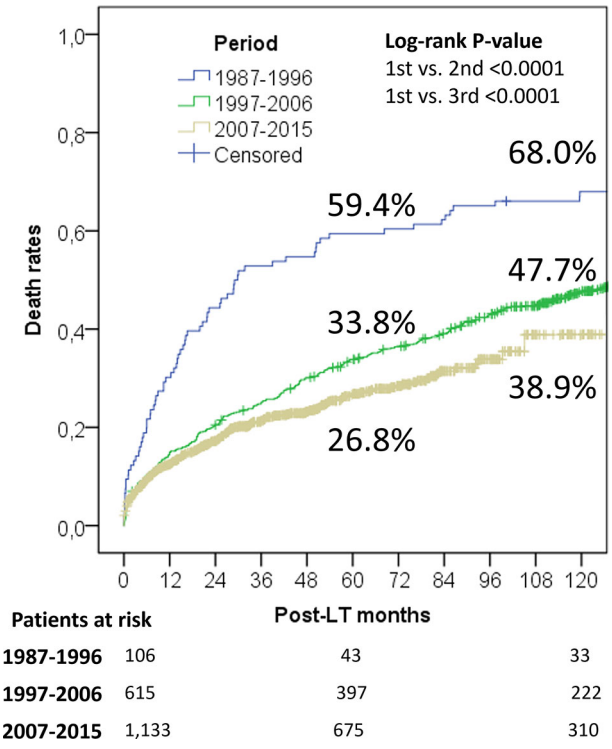

FIGURE 3 | Evolution of death rates (all the causes) in the different periods of transplantation.

cautious when declaring a patient cured from HCC if no recurrence has been diagnosed within 5 years after LT and also underlines the importance of a long-life oncologic follow-up (31).

Another interesting aspect to highlight is the fact that a high number of patients with HCC with recurrence were still alive at the time of last follow-up. This finding further underlines the role of screening protocols, which represent the only way to early diagnose and, whenever possible, aggressively treat the recurrence (32). In this setting, the beneficial role of the new systemic therapies is unexplored. However, the potential ability of these drugs to prevent or to manage mid- and long-term recurrence requires further attention (33, 34).

The study presents some limitations. First, this is a retrospective analysis, but the great majority of studies focusing on transplant oncology derive from retrospective cohorts. Second, this study is based on a large European experience with an extended enrolment period (1987–2015). Such a long-time span leads to several potential biases linked to a modified and improved tumor and patient management. The enrolment of patients transplanted during the earlier periods was necessary to document long-term oncologic results and patient survivals post-LT. To mitigate potential biases, the variable "era of LT" was introduced in the mathematical models, and several sub-analyses focused on the different periods were performed. The multicenter nature of the study is likely to add another bias due to some differences in relation to HCC policies in the different centers. The enrollment of large patient numbers should mitigate a "center-related" effect, minimizing the potential impairment caused by different waiting times, neo-adjuvant strategies, and center volumes. Moreover, the composition of this European collaborative group was based on a similar interest and approach toward patients with HCC selected for a potential liver transplantation (LT). Last, the inclusion criteria of patients with HCC for LT changed during the study period, moving from a "liberal" approach *via* the exclusive use of the Milan criteria to the more recent use of the expanded criteria. Therefore, the variable "LT era" was introduced in the mathematical models and a LT period–oriented analysis was also performed to look at the effect of changes in the treatment of HCC in potential liver patients.

In conclusion, LT generates long-term overall and disease-free survival rates which are superior to all other oncologic treatments of HCC. The role of LT in the modern treatment of HCC becomes even more valued when the follow-up period reaches at least 10 years. The results of LT continue to improve even when prudently widening the inclusion criteria for transplantation. Despite the fact that the incidence of HCC recurrence is highest during the first 5 years post-transplant, one-third of them occur later on, indicating the importance of a life-long follow-up of these patients.

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 AOU Policlinico Umberto I Rome. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QL and JL contributed to conception and design of the study. QL, AnV, SI, AlV, GM, SO, MH-L, MC, TM, FM, and GS contributed to acquisition of data. QL analyzed and interpreted the data. QL and JL drafted the article. SA, MV, GT, GM, JM, ET, MR, UC, BS, and JL critically revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.877107/full#supplementary-material

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Recurrence Patterns After Hepatectomy With Very Narrow Resection Margins for Hepatocellular Carcinoma

*Chih-Hsien Cheng[1], Yin Lai[2], Hao-Chien Hung[1], Jin-Chiao Lee[1], Yu-Chao Wang[1], Tsung-Han Wu[1], Chen-Fang Lee[1], Ting-Jung Wu[1], Hong-Shiue Chou[1], Kun-Ming Chan[1] and Wei-Chen Lee[1]**

[1]Division of Liver and Transplantation Surgery, Department of General Surgery, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan, [2]Department of General Surgery, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

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Edited by:
Alessandro Vitale, University Hospital of Padua, Italy

Reviewed by:
Liu Weiren, Fudan University, China
Weixing Guo, Eastern Hepatobiliary Surgery Hospital, China

***Correspondence:**
Wei-Chen Lee
weichen@cgmh.org.tw

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Background: The extent of hepatic resection In HCC depends on the remnant liver reserve or the proximity of the tumor to major vessels. In this study, we evaluated the effects of very close resection margins on postoperative recurrence.

Methods: Consecutive LR for HCC between 2003 and 2009 were studied. Patients were divided into groups with very narrow (≤1 mm) or wider (>1 mm) resection margins. Propensity score matching (PSM) was used to balance demographic, surgical, and pathological factors.

Results: 983 patients were included in the study. After PSM, 173 patients were analyzed in each group. 5-year tumor recurrence and survival rates were comparable. Most recurrences were multiple intrahepatic. Section margin recurrences were similar in both groups. By multivariate analysis, tumor size >5 cm was associated with a very narrow resection margin, whereas low platelet count and tumor macrovascular invasion were significant factors related to tumor recurrence.

Conclusions: Patients with very narrow surgical margins showed outcomes comparable to those with wider surgical margins. Most recurrences were multiple intrahepatic and associated with the degree of portal hypertension and adverse tumor biology. Although wide surgical margins should be aimed whenever possible, a narrow tumor-free margin resection still represents an effective therapeutic strategy.

Keywords: hepatocellu, hepatectomy, margin, recurrence pattern, recurrence factors

INTRODUCTION

Liver resection (LR) is the mainstay treatment for early hepatocellular carcinoma (HCC) patients. However, even after curative resections, HCC still shows a high recurrence rate (1–3). Among the surgical factors, resection margins have been extensively studied for their effects on postoperative recurrence. During surgery, a wide tumor-free margin is always attempted but the extent of hepatic

resection depends on the remnant liver reserve, the depth of the tumor location, and the proximity to major vascular structures (4). Moreover, the resection of excessive liver tissue during surgery may lead to liver dysfunction in patients with liver cirrhosis (5). Liver damage in patients with HCC after resection is also a risk factor associated with recurrence and poor prognosis (6–8).

While a positive surgical margin has a clear impact on oncological outcomes, the significance of close surgical margins remains controversial. Wide margins have been suggested for small (<5 cm) HCCs (9, 10), non-anatomic resections (11), and HCCs with microvascular invasion, without cirrhosis (12), or with high alpha-fetoprotein (AFP) levels (13). However, other investigations demonstrated that margins <1 cm (14) and tumor-negative margins of ≤1 mm had no impact on postoperative recurrence patterns and rates (15, 16).

In this study, we aim to explore the impact of very narrow surgical margins (≤1 mm) on tumor recurrence in patients with HCC who underwent hepatectomy.

MATERIAL AND METHODS

Patients

We retrospectively reviewed the records of patients who underwent LR for HCC at the Chang Gung Memorial Hospital at Linkou, Taiwan, between April 2003 and December 2009. We excluded the patients with intrahospital mortality, mixed type cholangio-hepatocellular carcinoma, fibrolamellar type hepatocellular carcinoma, surgical margin involvement, and post-op follow-up or non-cancer-related survival less than 1 year. The clinical data was obtained from the medical charts and the Taiwan Cancer Registry. The information comprised of the patients' demographics, preoperative laboratory examination, hepatitis serology, surgical features, pathologic features, postoperative complications, tumor staging, tumor recurrence, treatment of tumor recurrence, and the last following-update or date of death.

The study was approved by the institutional review board of the Chang Gung Memorial Hospital (IRB102-4474B).

Hepatectomy

The pre-operative diagnosis of HCC was based on the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver Disease (EASL) guidelines (17, 18).

The criteria for LR and the operative procedures were previously described (2, 5, 19). The extent of liver resection was assessed according to the indocyanine green retention rate at 15 min (ICG R_{15}). ICG R_{15} was performed by injecting 0.5 mg/kg of ICG into the patients' peripheral vein and drawing a blood sample from another site 15 min later to calculate the retained ratio of ICG. Patients with ICG_{15} exceeding 20% were carefully selected for major resections, defined as a resection of three or more hepatic segments.

The liver resections were performed using a conventional open approach. Intraoperative ultrasonography was routinely performed in order to confirm resectability and evaluate the relationship between the resection line and major vascular structures. Inflow control with the Pringle maneuver was commonly applied intermittently. Hemivascular control was performed in selected right or left hepatectomies. The liver parenchyma was divided according to the surgeon's preference using a clamp-crushing technique or ultrasonic dissector.

A surgical margin of at least 1 cm was aimed during surgery. However, when the tumor was near major vessels or the patients showed severe comorbidities and liver cirrhosis, a grossly negative macroscopic margin without exposure of the tumor was considered adequate (**Supplementary Figure S1**). The final resection margin was defined as the shortest microscopic distance from the edge of the tumor to the transection line by histological examination. A wide margin (WM) was defined as a margin >1 mm and a close margin (CM) as a margin ≤ of 1 mm.

Follow up

After surgery, all patients were followed-up every three months. Routine examinations included liver function tests, AFP level, and liver ultrasonography. When ultrasonography revealed a suspicious liver nodule or AFP levels were elevated, tri-phasic computed tomography (CT) or magnetic resonance imaging (MRI) were performed to look for any evidence of tumor recurrence.

The tumor recurrence rate was defined as the interval between the time of liver resection and the detection of recurrence by multiphasic computed tomography, magnetic resonance imaging, and hepatic angiography. The overall survival rate was defined as the interval between the surgery date and the time of death or last follow-up.

Statistical Analysis

Based on an increase in the 5-y tumor recurrence rate of 15% for narrow surgical margin as compared with that for wide surgical margin (14, 20) and assuming an α of 0.05 and a power of 0.80, each treatment group had to include at least 151 patients.

The continuous data were expressed as the median and interquartile ranges. The differences in continuous variables were assessed using Mann-Whitney U tests. The categorical variables were expressed as percentages and analyzed using chi-square tests.

The Kaplan-Meier method with log-rank test was applied to compare survival distributions.

Binary logistic regression was used to examine the variables associated with narrow surgical margins. The Cox proportional hazard regression model was applied to evaluate the risks of tumor recurrence and OS.

To minimize selection bias, a 1:1 propensity score matching (PSM) was performed using the nearest-neighbor method with a caliper size of 0.05. We included 18 relevant patient, surgical and tumor variables for propensity score generation. These variables included patients age, gender, hepatitis B and C status, platelet counts, albumin levels, Child status, ICG

retention rate at 15 min, AFP levels, the extent of LR, intraoperative blood loss, presence of cirrhosis, daughter nodules, microvascular invasion, macrovascular invasion, tumor ruptures, tumor sizes, tumor grading, and tumor/node/metastasis (TNM)/American Joint Committee on Cancer (AJCC) staging system. After propensity score adjustment, both therapy groups were checked again for heterogeneity in covariates with Mann–Whitney U tests. $\eta 2$ was calculated to confirm the matching balance. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS® (SPSS, Chicago, Illinois, USA).

RESULTS

Patients

From April 2003 to December 2009, 1,116 patients underwent open liver resection for suspected HCC. After excluding the patients with other diagnoses, in-hospital mortality, surgical margin involvement, and follow-ups of less than 1 year, we included 983 patients in the analysis.

Seven hundred and ten and 273 patients displayed WM and CM, respectively. The median follow-up duration was 85 months (range, 12–196 months) and the last follow-up occurred in September 2019 (**Figure 1**). After PSM, 173 patients were allocated in each group.

Before PSM, the two groups did not show any differences in the pre-operative factors. The median age of the patients was 58 years old, 79.3% were male, and 63.1% displayed HBV infection. Among the patients, 45.1% had liver cirrhosis, 24.6% tumor microvascular invasion, 4.2% macrovascular invasion, and 11.1% daughter nodules. The median tumor size was 3.5 cm. According to the distribution of TNM staging, we observed that 18.2% of the patients were in stage Ia, 49.4% in stage Ib, 16.2% in stage II, 6.6% in stage IIIa, 9.5% in stage IIIb, and 0.1% in stage IVa. In relation to the surgical and tumor factors, the CM group displayed significantly greater intraoperative blood loss ($p < 0.001$) and tumor sizes ($p =$

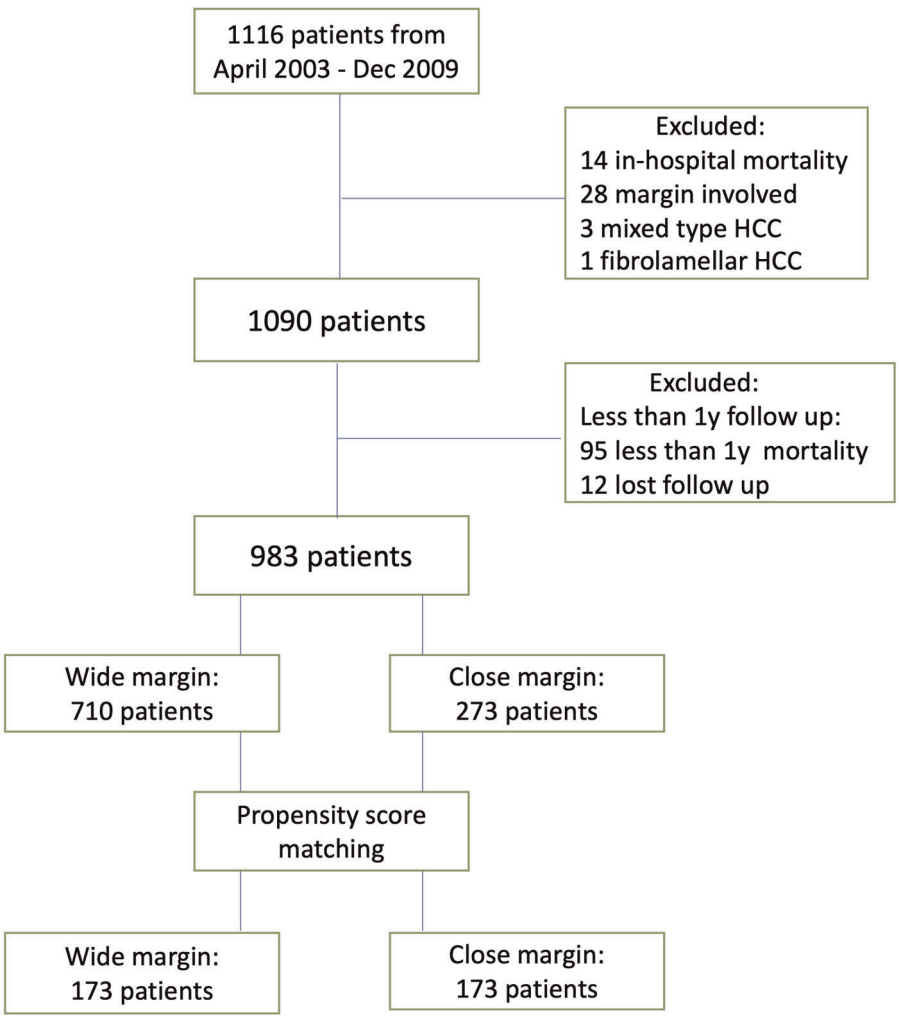

FIGURE 1 | Flow chart of the study cohort.

TABLE 1A | Patient characteristics before PSM.

Variable	Before PSM			
	Wide margin ($n = 710$)	Close margin ($n = 273$)	p-value	η^2 value
Patient factors				
Age (years)	57.00 (48.00–67.00)	60.00 (48.50–68.00)	0.171	0.002
Gender				
Male	556 (78.3)	224 (82.1)	0.194	0.001
Female	154 (21.7)	49 (17.9)		
HBsAg				
Positive	399 (63.0)	154 (63.4)	0.925	<0.001
Negative	234 (37.0)	89 (36.6)		
Anti HCV ab				
Positive	211 (36.5)	71 (34.0)	0.513	<0.001
Negative	367 (63.5)	138 (66.0)		
Platelets (10^9/L)	175 (127.50–215.00	171 (130.00–220.75)	0.490	<0.001
INR	1.09 (1.00–1.10)	1.08 (1.00–1.11)	0.986	<0.001
AST (U/L)	35.00 (26.00–56.00)	39.50 (25.00–60.75)	0.111	0.003
ALT (U/L)	39.00 25.00–66.00)	41.00 (24.00–72.00)	0.760	<0.001
Albumin (g/dl)	4.20 (3.90–4.42)	4.10 (3.90–4.40)	0.068	0.003
Total bilirubin (mg/dl)	0.70 (0.60–0.90)	0.80 (0.60–1.00)	0.053	0.004
AFP (ng/ml)	19.20 (5.50–243.00)	26.00 (5.22–294.10)	0.678	<0.001
ICG-R15	7.03 (4.11–11.58)	7.72 (4.59–12.51)	0.061	0.004
Child -Pugh status				
B	10 (1.4)	2 (0.7)	0.378	<0.001
A	700 (98.6)	271 (99.3)		
Surgical factors				
Extent of resection				
Major	104 (14.6)	42 (15.4)	0.771	0.002
Minor	606 (85.4)	231 (84.6)		
Anatomic resection				
Yes	139 (19.6)	63 (23.1)	0.224	0.001
No	571 (80.4)	210 (76.9)		
Blood loss (ml)	200.00 (100.00–400-00)	300.00 (100.00–500.00)	<0.001	0.013
Tumor factors				
Cirrhosis				
Yes	325 (45.8)	118 (43.2)	0.472	<0.001
No	385 (54.2)	155 (56.8)		
Tumor size (cm)	3.50 (2.10–5.50)	3.80 (2.40–6.90)	0.004	0.009
Daughter nodules				
Yes	75 (10.6%)	34 (12.5)	0.398	<0.001
No	635 (89.4)	239 (87.5)		
Microvascular invasion				
Yes	169 (23.8)	73 (26.7)	0.338	0.001
No	541 (76.2)	200 (73.3)		
Macrovascular invasion				
Yes	30 (4.2)	11 (4.0)	0.890	<0.001
No	680 (95.8)	262 (96.0)		

(*continued*)

TABLE 1A | Continued

Variable	Before PSM			
	Wide margin ($n = 710$)	Close margin ($n = 273$)	p-value	η^2 value
Tumor grading				
III/IV	277 (39.1)	106 (39.0)	0.977	<0.001
I/II	432 (60.9)	166 (61.0)		
TNM staging				
IA	140 (19.7)	39 (14.3)	0.142	0.002
IB	345 (48.6)	141 (51.6)		
II	117 (16.5)	42 (15.4)		
IIIA	42 (5.9)	23 (8.4)		
IIIB	66 (9.3)	27 (9.9)		
IVA	0	1 (0.4)		

Variables are expressed as median (interquartile range) or as number (n) and percent (%). Abbreviations: PSM, propensity score matching; HBsAg, hepatitis B surface antigen; HCV ab, hepatitis C virus antibody; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 min; TNM, tumor-nodal-metastasis.

TABLE 1B | Patient characteristics after PSM.

Variable	After PSM			
	Wide margin ($n = 173$)	Close margin ($n = 173$)	p value	η^2 value
Patient factors				
Age (years)	58.00 (50.00–68.00)	61.00 (52.00–69.00)	0.482	0.001
Gender				
Male	139 (80.3)	137 (79.2)	0.789	<0.001
Female	34 (19.7)	36 (20.8)		
HBsAg				
Positive	96 (56.1)	98 (57.3)	0.827	0.001
Negative	75 (43.9)	73 (42.7)		
Anti HCV ab				
Positive	52 (31.9)	53 (31.9)	0.096	0.006
Negative	111 (68.1)	113 (68.1)		
Platelets (10^9/L)	180.00 (130.50–221.50)	182.00 (137.00–227.00)	0.426	0.002
INR	1.06 (1.00–1.10)	1.08 (1.00–1.10)	0.737	<0.001
AST (U/L)	33.00 (25.00–50.00)	40.00 (24.50–63.50)	0.112	0.007
ALT (U/L)	33.00 (21.00–57.00)	41.00 (23.00–72.50)	0.091	0.008
Albumin (g/dl)	4.20 (3.85–4.50)	4.10 (3.90–4.40)	0.456	0.002
Total bilirubin (mg/dl)	0.80 (0.60–1.00)	0.80 (0.60–1.00)	0.834	<0.001
AFP (ng/ml)	13.21 (5.00–183.50)	28.70 (5.95–335.45)	0.065	0.01
ICG-R15	6.79 (4.29–10.44)	7.13 (4.60–12.16)	0.182	0.005
Child -Pugh status				
B	4 (2.3)	2 (1.2)	0.41	<0.001
A	169 (97.7)	171 (98.8)		
Surgical factors				
Extent of resection				
Major	29 (16.8)	34 (19.7)	0.486	0.001
Minor	144 (83.2)	139 (80.3)		

(*continued*)

TABLE 1B | Continued

Variable	After PSM			
	Wide margin ($n = 173$)	Close margin ($n = 173$)	p value	η^2 value
Anatomic resection				
Yes	34 (19.7)	33 (19.1)	0.892	<0.001
No	139 (80.3)	140 (80.9)		
Blood loss (ml)	200.00 (100.00–500.00)	300.00 (100.00–500.00)	0.135	0.014
Tumor factors				
Cirrhosis				
Yes	75 (43.4)	65 (37.6)	0.273	0.002
No	98 (56.6)	108 (62.4)		
Tumor size (cm)	3.50 (2.20–6.00)	4.20 (2.50–8.30)	0.089	0.019
Daughter nodules				
Yes	19 (11.0)	21 (12.1)	0.737	<0.001
No	154 (89.0)	152 (87.9)		
Microvascular invasion				
Yes	40 (23.1)	45 (26.0)	0.532	0.001
No	133 (76.9)	128 (74.0)		
Macrovascular invasion				
Yes	5 (2.9)	4 (2.3)	0.736	<0.001
No	168 (97.1)	169 (97.7)		
Tumor grading				
III/IV	57 (32.9)	68 (39.3)	0.218	0.003
I/II	116 (67.1)	105 (60.7)		
TNM staging				
IA	35 (20.2)	22 (12.7)	0.247	0.004
IB	82 (47.4)	92 (53.2)		
II	31 (17.9)	26 (15.0)		
IIIA	11 (6.4)	18 (10.4)		
IIIB	14 (8.1)	14 (8.1)		
IVA	0	1 (0.6)		

Variables are expressed as median (interquartile range) or as number (n) and percent (%). Abbreviations: PSM, propensity score matching; HBsAg, hepatitis B surface antigen; HCV ab, hepatitis C virus antibody; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; TNM, tumor-nodal-metastasis.

0.01) (**Supplementary Table S1**). However, after adjusting for propensity scores, blood loss and tumor sizes were comparable between the two groups (**Table 1**).

When we analyzed the risk factors associated with CM resections, the univariate and multivariate analysis showed that a tumor size ≥ of 5 cm was the only independent prognostic factor (**Table 2**).

Tumor Recurrence Rates

Before PSM, the recurrence rates (RR) were significantly higher in the CM group than in the WM group. The median 5-years RR were 63.7% vs. 54.7% and the median 10-years RR were 69% vs. 72.7% ($p = 0.014$) in the CM and WM groups, respectively (**Figure 2A**). Following PSM, the RR were not statistically different between the two groups. The median 5-years RR were 54.6% and 63.4% and the median 10-years RR were 69.5% and 72.5% ($p = 0.155$) in the CM and WM groups, respectively (**Figure 2B**).

Risks Factor for Tumor Recurrence

After PSM, by univariate analysis, we observed that a low platelet count (platelet count ≤100,000/μl), a tumor size ≥ of 5 cm, the presence of daughter nodules, tumor macrovascular invasion, and tumor TNM staging were significant prognostic factors for tumor recurrence. The multivariate analysis showed that a low platelet count and the presence of tumor macrovascular invasion were the only significant factors for tumor recurrence (**Table 3**).

TABLE 2 | Risks factors for close resection margin.

	Univariate		Multivariate	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Patient factors				
Age (years)				
≥70 vs. <70	1.199 (0.707–2.034)	0.501		
Platelets (10^9/l)				
≤100 vs. >100	1.356 (0.682–2.296)	0.386		
AFP (ng/ml)				
³800 vs. <800	0.574 (0.321–1.027)	0.062		
³400 vs. <400	0.708 (0.422–1.188)	0.191		
³20 vs. <20	0.706 (0.463–1.078)	0.100		
ICG-R15				
³20 vs. <20	1.400 (0.549–3.571)	0.481		
Child-P vs. Pugh status				
B vs. A	2.024 (0.366–11.196)	0.419		
Surgical factors				
Extent of resection				
Major vs. Minor	0.794 (0.461–1.369)	0.407		
Type of resection				
Anatomical vs. nonanatomical	0.782 (0.432–1.415)	0.417		
Blood loss (ml)				
³1,000 vs. <1000	0.697 (0.301–1.615)	0.399		
Pathological factors				
Cirrhosis				
Yes vs. No	1.211 (0.788–1.859)	0.382		
Tumor size (cm)				
³5 vs. <5	1.779 (1.131–2.797)	0.013	1.725 (1.094–2.721)	0.019
Capsule				
No vs. Yes	0.956 (0.533–1.717)	0.881		
Daughter nodules				
Yes vs. No	0.847 (0.440–1.628)	0.618		
Macrovascular invasion				
Yes vs. No	1.257 (0.332–4.764)	0.736		
Tumor rupture				
Yes vs. No	0.870 (0.308–2.453)	0.792		

Abbreviations: AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 min.

Patterns of Tumor Recurrence and Patient Survival

We observed that 43.9% of the patients developed single intrahepatic recurrence, 48.8% experienced multiple intrahepatic recurrences, and 7.3% displayed distant metastasis without intrahepatic recurrence. The patterns of tumor recurrence were not significantly different between the CM and WM patients. When we further evaluated the impact of close resection margins on section margin recurrence (recurrence at ≤1 cm from the resection margin regardless of whether there was any simultaneous intra- or extrahepatic recurrence) or early recurrence (recurrence ≤1 year), we also did not find any significant difference between the two groups (**Table 4**). Finally, the long-term OS was similar between the two groups. The 5-year and 10-year survival rates were 67.5% and 52.2% in the CM group and 74.3% and 54.9% in the WM group ($p = 0.160$), respectively (**Supplementary Figure S2**). For the patients with tumor microvascular invasion, satellite nodules or tumor macrovascular invasion, there were also no significant differences in recurrence and survival rates between the two groups (**Supplementary Figure S3**).

DISCUSSION

A wide tumor-free margin is paramount during oncological resections to avoid residual tumors at the resection site to promote tumor recurrence. However, during liver resections for HCC, wide surgical margins are limited by the presence of portal hypertension or liver cirrhosis. Additionally, major hepatic resections are associated with increased morbidity. Likewise, the tumors close to major hepatic veins or branches of the Glisson's pedicles are detached from the vessels with CUSA® and a sufficient surgical margin is sacrificed to preserve more liver parenchyma. Therefore, we conducted the present study to investigate the impact of very close margins on the outcome of patients with HCC undergoing resection.

Patients with HCC differ considerably in their baseline liver function and tumor characteristics. To reduce confounding variables and equate the treatment groups, we conducted PSM in 983 patients with long-term follow up. After a median follow-up of 85 months, our study did not show any statistical differences in tumor recurrence rates in the close and wide resection groups. By multivariate analysis, we also found that a low platelet count and the presence of tumor macrovascular invasion were the only independent prognostic factors, which underscores the impact of patients' characteristics and tumor biology on surgical factors.

The prognostic significance of wide surgical margins has been addressed in many previous studies with different cutoff values ranging from 2 cm to no margin. Poon et al. analyzed patients with <1 cm and ≥1 cm resection margins and the two groups showed comparable recurrence rates (14). On multivariate analysis, the authors found that only a pTNM stage of III/IV and perioperative transfusions were significant risk factors of tumor recurrence. Oguro et al. did not show

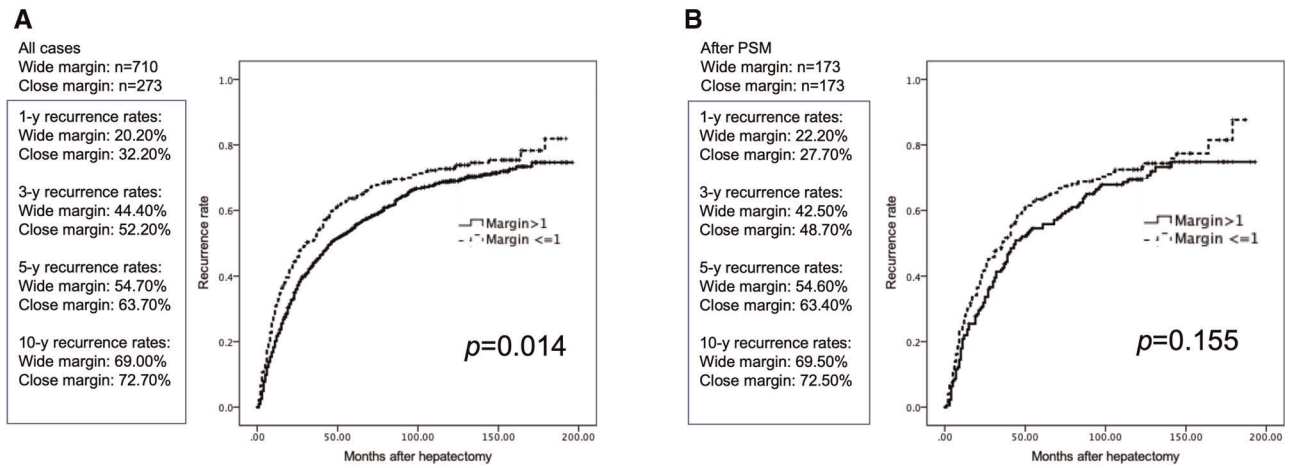

FIGURE 2 | Cumulative postoperative tumor recurrence rates in patients with margin >1 and ≤1 mm. (**A**) Before PSM. (**B**) After PSM.

any difference in the recurrence-free and overall survival of HCC patients undergoing macroscopic no-margin hepatectomy. Although a microscopically positive surgical margin was more frequent in the no-margin hepatectomy group than the control group, a microscopically positive margin was not associated with a higher incidence of recurrence in the remnant liver (15). Similarly, in another study investigating HCC patients who underwent resection with exposure of the tumor surface, the authors did not show any significant differences in the recurrence and survival rates between the tumor exposure group and the non-exposure group (21). Notably, the influence of tumor encapsulation was not observed in close marginal resections. In our study, we also did not find any correlation between the presence of tumor capsule and postoperative outcomes.

Several reports showed that the width of the resection margins had no impact on tumor recurrence or patient survival. However, several other studies also associated improved outcomes with wider surgical margins (12, 22, 23). Nara et al. categorized the patients according to the macroscopic appearance of HCC and reported that a wide resection resulted in better recurrence-free survival in patients with non-simple nodular type tumors without cirrhosis (20). However, the recurrence-free survival rates were not affected by the type of resection in patients with cirrhosis. The only prospective randomized trial that stratified the patients according to surgical margins (1 or 2 cm) advocated that wider margins gave a survival advantage only to the patients with HCC ≤2 cm (10). However, the group of patients with the survival advantage was very small (i.e., wide margins 12 patients, narrow margins 10 patients) and the margins width did not show any significant impact on tumor recurrence, regardless of HCC size.

Recurrences after surgery are mostly intrahepatic (24–26) and wide resections are aimed to avoid recurrences at the resection site. A previous study examined the patterns of intrahepatic micrometastases using large pathologic sections on liver specimens with ample resection margins and reported that the spread of micrometastases ranged from 0.05 to 6.1 cm (27). This supports the concept that extensive anatomic resections can achieve better tumor clearance by removing tumor-bearing portal territories. However, tumors can propagate proximally and distally after microscopic portal vein invasion (28) and the tumor dissemination can involve nonadjacent hepatic segments (29, 30). Additionally, tumor recurrence may also result from metachronous tumors that arise in the oncogenic cirrhotic liver (31–33). Therefore, even with extensive resections, it is difficult to eliminate the disease in every patient. In this study, most recurrences occurred in distal liver segments or multiple segments regardless of the margin width. This suggests that most recurrences were due to intrahepatic distant metastasis or multicentric carcinogenesis. In our study, overall 48.8% of the tumor recurrences were multiple intrahepatic recurrences and close resection margins were not associated with increased recurrences. In addition, early tumor recurrence is another concern after surgery for HCC, and is a leading cause of death within 2 years (34). Previously reported risk factors of early tumor recurrence included vascular invasion and positive margins (34) but the extension and the type of resection did not show any correlation with the risk of recurrence provided that the surgery was radical (3). In this study, the rates of early tumor recurrence were similar between the two section margin groups and even the subgroup of patients with section margin recurrences.

Our study has several limitations. As a retrospective study, confounding variables and selection bias cannot be fully eliminated even after PSM. Furthermore, to achieve a sufficiently long follow-up, we included patients who underwent liver resections before 2009. As a result, we did not include patients who underwent laparoscopic resections

TABLE 3 | Risks factors for tumor recurrence.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Patient factors				
Age (years)				
³70 vs. <70	1.071 (0.783–1.464)	0.668		
Gender				
Male vs. Female	1.184 (0.854–1.641)	0.311		
HBsAg				
Positive vs. Negative	1.154 (0.893–1.490)	0.273		
Anti HCV ab				
Positive vs.Negative	1.115 (0.851–1.462)	0.430		
Platelets (10^9/l)				
≤100 vs. >100	1.489 (1.025–2.163)	0.036	1.617 (1.094–2.390)	0.016
AFP (ng/mL)				
³800 vs. <800	1.211 (0.871–1.685)	0.254		
³400 vs. <400	1.135 (0.841–1.533)	0.407		
³20 vs. <20	1.247 (0.971–1.600)	0.084		
ICG-R15				
³20 vs. <20	1.080 (0.640–1.821)	0.773		
Child- Pugh				
B vs. A	1.424 (0.587–3.455)	0.435		
Surgical factors				
Extent of resection				
Major vs. Minor	1.151 (0.833–1.592)	0.393		
Blood loss (ml)				
³1,000 vs. <1000	1.241 (0.776–1.982)	0.367		
Margin (mm)				
≤1 vs. >1	1.197 (0.932–1.536)	0.159		
<5 vs. ≥5	1.538 (1.168–2.026)	0.002		
<10 vs. ≥10	1.571 (1.123–2.198)	0.008		
Pathological factors				
Cirrhosis				
Yes vs. No	1.220 (0.949–1.570)	0.121		
HAI				
³8 vs. <8	1.094 (0.700–1.712)	0.693		
Tumor size (cm)				
³10 vs. <10	1.366 (0.946–1.971)	0.096		
³5 vs. <5	1.375 (1.060–1.784)	0.016		
Capsule				
No vs. Yes	0.782 (0.539–1.134)	0.195		
Severe tumor necrosis				
No vs. Yes	0.504 (0.573–1.314)	0.504		
Severe fatty liver				
Yes vs. No	0.476 (0.152–1.493)	0.203		
Daughter nodules				
Yes vs. No	2.119 (1.491–3.011)	<0.001		
Microvascular invasion				
Yes vs. No	1.603 (1.213–2.118)	0.001		
Macrovascular invasion				
Yes vs. No	2.856 (1.403–5.816)	0.004	2.513 (1.016–6.213)	0.046
Tumor rupture				
Yes vs. No	1.140 (0.638–2.036)	0.659		
Tumor grading				
III/IV vs. I/II	1.216 (0.940–1.573)	0.137		
TNM staging (vs. Ia)		0.001		
Ib	1.099 (0.759–1.592)	0.616		
II	1.644 (1.058–2.553)	0.027		
IIIa	2.326 (1.414–3.825)	0.001		
IIIb	1.805 (1.064–3.064)	0.029		
IV	3.215 (0.439–23.564)	0.250		

Abbreviations: HBsAg, hepatitis B surface antigen; HCV ab, hepatitis C virus antibody; AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 min; HAI, hepatitis activity index; TNM, tumor-nodal-metastasis.

because this approach was not widely performed before 2009. Additionally, the histological and genetic features of the recurrent tumors were not analyzed or compared with the

TABLE 4 | Patterns of tumor recurrence.

Recurrence pattern (%)		Type of resection % (*n*)		*P*-value
Single intrahepatic	43.9	Wide margin	42.6 (46)	0.135
		Close margin	57.4 (62)	
Multiple intrahepatic	48.8	Wide margin	50.8 (46)	0.380
		Close margin	49.2 (59)	
Only distant metastasis	7.3	Wide margin	61.1 (11)	0.246
		Close margin	38.9 (7)	
Section margin recurrence	22.8	Wide margin	48.2 (27)	0.966
		Close margin	51.8 (29)	
Early (<1y) recurrence	35	Wide margin	55.8 (48)	0.384
		Close margin	44.2 (38)	
Early section margin recurrence	26.7	Wide margin	53.3 (8)	1.000
		Close margin	46.6 (7)	

primary tumors, so as to classify as intrahepatic metastases or *de novo* hepatocarcinogenesis, which would provide a better insight into real tumor-free resection margins.

In conclusion, the patients with very narrow surgical margins showed outcomes comparable to those with wider margins. Most recurrences were multiple intrahepatic recurrences related to the degree of portal hypertension and adverse tumor biology. Although wide surgical margins should be whenever possible, a narrow tumor-free margin resections still represent an effective therapeutic strategy.

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 study was approved by the institutional review board of the Chang Gung Memorial Hospital (IRB102-4474B). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CHC: drafting the manuscript and data collection. CHC, YL, HCH, JCL, YCW, THW, CFL: data collection, TJW, HSC, KMC and WCL designing and revising the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.926728/full#supplementary-material.

Supplementary Figure 1 | Abdominal computed tomography and intraoperative images of tumors overriding the middle hepatic vein (**A**) or the porta hepatis (**B**). The tumors were detached from the major vessels without a macroscopic margin.

Supplementary Figure 2 | Cumulative postoperative patient survival rates in patients with margin >1 and ≤1 mm after PSM.

Supplementary Figure 3 | Cumulative postoperative tumor recurrence and patient survival rates in patients with tumor microvascular invasion (**A**), satellite nodules (**B**) and tumor macrovascular invasion (**C**) according to margin >1 and ≤1 mm.

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EDITED BY
Alessandro Vitale,
University Hospital of Padua, Italy

REVIEWED BY
Dario Lorenzin,
University Hospital Of Udine, Italy
Alessandra Bertacco,
Padua University Hospital, Italy
Davide Ghinolfi,
Pisana University Hospital, Italy

*CORRESPONDENCE
Salvatore Gruttadauria
sgruttadauria@ismett.edu

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How important is the role of iterative liver direct surgery in patients with hepatocellular carcinoma for a transplant center located in an area with a low rate of deceased donation?

Duilio Pagano[1], Simone Khouzam[2], Bianca Magro[1], Marco Barbara[3], Davide Cintorino[1], Fabrizio di Francesco[1], Sergio Li Petri[1], Pasquale Bonsignore[1], Sergio Calamia[1], Giacomo Deiro[1], Calogero Cammà[4], Marco Canzonieri[1] and Salvatore Gruttadauria[1,5]*

[1]Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto di Ricovero e Cura a Carattere Scientifico-Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione), UPMC (University of Pittsburgh Medical Center), Palermo, Italy, [2]Department of Surgery, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, United States, [3]Research Department, IRCCS-ISMETT (Istituto di Ricovero e Cura a Carattere Scientifico - Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy, [4]Section of Gastroenterology & Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy, [5]Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy

Introduction: Hepatocellular carcinoma (HCC) accounts for nearly 90% of primary liver cancers, with estimates of over 1 million people affected by 2025. We aimed to explore the impacting role of an iterative surgical treatment approach in a cohort of HCC patients within the Milan criteria, associated with clinical risk factors for tumor recurrence (RHCC) after liver transplant (LT) and loco-regional therapies (LRT), as well as liver resection (LR) and/or microwave thermal ablation (MWTA).

Methods: We retrospectively analyzed our experience performed during an 8-year period between January 2013 and December 2021 in patients treated for HCC, focusing on describing the impact on preoperative end-stage liver disease severity, oncologic staging, tumor characteristics, and surgical treatments. The Cox model was used to evaluate variables that could predict relapse risks. Relapse risk curves were calculated according to the Kaplan–Meier method, and the log-rank test was used to compare them.

Results: There were 557 HCC patients treated with a first-line approach of LR and/or LRTs (*n* = 335) or LT (*n* = 222). The median age at initial transplantation was 59 versus 68 for those whose first surgical approach was LR and/or LRT. In univariate analysis with the Cox model, nodule size was the single predictor of

recurrence of HCC in the posttreatment setting (HR: 1.61, 95% CI: 1.05–2.47, p = 0.030). For the LRT group, we have enlightened the following clinical characteristics as significantly associated with RHCC: hepatitis B virus infection (which has a protective role with HR: 0.34, 95% CI: 0.13–0.94, p = 0.038), number of HCC nodules (HR: 1.54, 95% CI: 1.22–1.94, p < 0.001), size of the largest nodule (HR: 1.06, 95% CI: 1.01–1.12, p = 0.023), serum bilirubin (HR: 1.57, 95% CI: 1.03–2.40, p = 0.038), and international normalized ratio (HR: 16.40, 95% CI: 2.30–118.0, p = 0.006). Among the overall 111 patients with RHCC in the LRT group, 33 were iteratively treated with further curative treatment (12 were treated with LR, two with MWTA, three with a combined LR-MWTA treatment, and 16 underwent LT). Only one of 18 recurrent patients previously treated with LT underwent LR. For these RHCC patients, multivariable analysis showed the protective roles of LT for primary RHCC after IDLS (HR: 0.06, 95% CI: 0.01–0.36, p = 0.002), of the time relapsed between the first and second IDLS treatments (HR: 0.97, 95% CI: 0.94–0.99, p = 0.044), and the impact of previous minimally invasive treatment (HR: 0.28, 95% CI: 0.08–1.00, p = 0.051).

Conclusion: The coexistence of RHCC with underlying cirrhosis increases the complexity of assessing the net health benefit of ILDS before LT. Minimally invasive surgical therapies and time to HCC relapse should be considered an outcome in randomized clinical trials because they have a relevant impact on tumor-free survival.

KEYWORDS

liver transplantation, laparoscopic, liver resection, hepatocellular carcinoma, thermal ablation

Introduction

Hepatocellular carcinoma (HCC) accounts for nearly 90% of primary liver cancers, with over 1 million people affected by 2025 (1). Since 2018, HCC has remained the sixth most common cancer and the third most fatal cancer globally (2, 3). Liver resection (LR), liver transplant (LT), and thermal ablations are the curative surgical treatment options for HCC, but each option depends on the number of nodules, tumor diameter, vascular invasion, extrahepatic disease, and shortage of deceased donor pool for LT.

The Barcelona Clinic Liver Cancer (BCLC) classification system has been approved by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association, and the European Association for the Study of the Liver (EASL) to indicate a specific therapeutic option for HCC at each. Resection is recommended for those at BCLC stage 0 or BCLC-A with a solitary nodule (4, 5). Additionally, the patient must be an optimal candidate meeting the following criteria: compensated Child–Pugh class A liver function, model for end-stage liver disease (MELD) score of <10, and matched grade portal hypertension (4, 6, 7). In Asia, the classification system is designed to detect HCC earlier with higher sensitivity and lower specificity (8). The Korean Liver Cancer Association - National Cancer Center revised its guidelines in 2018 to advise the management of early HCC with early treatment, such as local-regional ablations or trans-arterial chemoembolization (TACE) (9, 10). Still, the median OS for treated HCC is ≥60 months, with a 5-year survival rate approaching 70%; HCC recurrence (RHCC) develops in nearly 70% of patients within 5 years after initial resection (1).

LT is the definitive treatment option for HCC patients within the eligible Milan criteria, but LT must be safeguarded with consideration given to LR before LT due to the possibility of recurrence, waiting list times, and limited organ supply (10–13). Of note, the Italian organ allocation system differs from MELD such that it is a blended model of urgency, utility, and transplant benefit (14, 15). Regardless, there remains a high likelihood, 6%–18%, of RHCC, with 40% to 50% occurring within the first year after LT and 20% occurring during the second year (16, 17). Immunosuppressive regimens and surgical decision-making should also consider the fractional allele imbalance as it provides critical information on the risk of HCC recurrence

(18). Given the high likelihood of RHCC, consideration of posttransplant recurrence and outcomes must be considered (19, 20).

Well-known predictors of poor prognosis after LR are diameter of ≥5 cm, multiple tumors, no capsular formation, vascular invasion, TNM classification stage 3 or 4, and alpha-fetoprotein (AFP) of at least 32 ng/ml (21–23). Similarly, risk factors for RHCC with open LR followed by LT were determined to be elevated AFP levels, microvascular invasion, tumor grade, and multinodular tumors. However, instead of primary LT or open LR, laparoscopic liver resection (LLR) and ablation before LT are the new preferred treatment approaches due to the significant improvements in survival and patient outcomes (24–27). This study aims to describe our experience in applying the iterative treatment approach to a cohort of HCC patients within the Milan criteria and to explore the role of surgical management and clinical risk factors that could impact RHCC and OS after LT.

Materials and methods

Here, we report a series of HCC patients' management and treatments at the Mediterranean Institute for Transplantation and Highly Specialized Therapies (ISMETT) center with the aim of analyzing RHCC in terms of associated risk factors and best treatment options in those treated with iterative liver direct surgery strategy (ILDS) as LR and loco-regional therapy (LRT), during an 8-year period between January 2013 and December 2021. All data were collected using the electronic database and processed retrospectively. The diagnosis of HCC was made in the period before undergoing locoregional procedures, receiving an LR and/or LRT, or being listed for LT, following the criteria of the main AASLD and EASL-EORTC Clinical Practice Guidelines (28, 29). LT included both living and deceased donors, with one donor having died of cardiac death. Patients receiving living-donor LT, however, were not included in the following analysis. The surgical treatment option was selected after a careful multidisciplinary evaluation of the patient and considering staging, tumor location, and residual liver function (30). Before operating, the criteria for judging patients suitable for HCC resection were as follows: (1) BCLC 0/A (no macrovascular invasion or distant/lymphatic metastasis); (2) Child–Pugh grade A/B. Patients who did not meet the LR or LLR criteria were then considered for percutaneous microwave thermal ablation (MWTA). In cases where HCC nodules were challenging to approach percutaneously or in patients with moderated ascites, MWTAs were performed with a laparoscopic approach (LMWTA). The remaining subset of HCC patients underwent a transplant evaluation and were only included in the list after radiological confirmation of compliance with the Milan criteria (single nodule ≤5 cm or up to three nodules each ≤3cm, in the absence of macrovascular infiltration and distant metastases). In some doubtful cases, it was also necessary to perform a biopsy examination.

Patients with a diagnosis of RHCC were only considered for LT if the HCC fell within the Milan criteria and were able to meet the other transplant evaluation criteria. After surgical procedures, all patients underwent a follow-up protocol every 3 months for the first year and twice per year thereafter. The protocol included serum levels of AFP, ultrasonography, abdomen computed tomography (CT) with contrast medium, and/or magnetic resonance imaging (MRI) with hepato-specific contrast medium. In cases of ascertained or suspected recurrence of intrahepatic and/or extrahepatic HCC, other investigations were performed: liver MRI, chest CT, bone scan, ultrasound-guided biopsy, or positron emission tomography (PET). The parameters evaluated in the recruited patients are the number of liver lesions compatible with HCC, the site, the maximum size of the tumor, the presence or absence of angiolymphatic invasion, the execution of previous LRTs, the tumor histologic type, and tumor recurrence. Whenever necessary, patients underwent bridging or downstaging procedures (TACE or percutaneous ablations) in an attempt to maintain the patient's suitability for LT.

The clinical endpoint of this study was time to RHCC after first-line treatment and time to further RHCC after an iterative treatment. We also evaluated patients' overall survival after LT.

Statistical analysis

Patients' characteristics are summarized as the median and interquartile range (IQR) or as frequency and percentage, as appropriate. Overall survival and time to recurrence were estimated by means of Kaplan–Meier estimators and tested for differences by means of Log-rank tests. Time to recurrence was defined as the number of days between the transplant and the first radiological evidence of tumor recurrence. The proportional hazard (PH) assumption between LR/MWTA group and LT was tested both graphically, through a complementary log–log transformation of survival curves, and parametrically, by testing the slope of Schoenfeld residuals with respect to survival times (Harrell–Lee test). Whenever the PH assumption did not hold, PH Cox models were then stratified with respect to the treatment group. A multivariable model was selected by means of a forward stepwise regression algorithm using the Akaike information criterion as a stopping rule. All hypotheses were tested at $\alpha = 0.05$ significance level. All analyses and graphics were performed using the R statistical environment, version 4.1.2.

Results

Study population

Between January 2013 and December 2021, 597 patients with a recent diagnosis of HCC were judged to be eligible for surgical

curative treatment among those referred to our institution for surgical evaluation. Of these, 335 were suitable for LR or thermal ablation, three underwent a living-donor LT, and 259 entered the waiting list for LT (Figure 1). Thirty-seven patients were subsequently removed from the waiting list due to disease worsening or death, the remaining 222 underwent a deceased-donor LT. Table 1 presents the clinical characteristics of 557 patients who were surgically treated for HCC either with a LR and/or MWTA ($N = 335$) or with a deceased-donor LT ($N = 222$).

The LR/MWTA group accounted for 335 patients; of these, 255 were men (76%), and 80 were women (24%); 266 (79%) were treated with LR, 50 (15%) with MWTA, and 19 (6%) with a combined LR/MWTA treatment. A minimally invasive method of LLR or LMWTA was preferred whenever possible and used 53% of the time. Most of the patients in the LR/MWTA group had very well-compensated liver disease. In particular, 315 (94%) patients were in Child–Pugh class A, 20 (6%) were in class B, and no patients were in Child–Pugh class C.

The median clinical MELD-Na score was 9 (IQR: 8–10) at the time of treatment. On imaging techniques, 253 patients (76%) had monofocal HCC, 63 patients (19%) had bifocal HCC, and 19 patients (6%) had up to three HCC nodules. In addition, histological grading was analyzed according to the Edmonson and Steiner classification (G1: well-differentiated, G2: moderately differentiated, G3: poorly differentiated, G4: undifferentiated) and 65% ($N = 217$) of patients presented with well- or moderately differentiated HCC, while 35% ($N = 118$) had a poorly differentiated HCC. Tumor sizes were histologically classified (pT) as T1 in 162 cases (48%), T2 in 127 cases (38%), and T3 in the remaining 46 (14%). The microvascular invasion was found in 33% ($N = 112$) of the LR/MWTA group patients. Thirty-three patients (10%) underwent a second surgical treatment due to RHCC, almost half of whom (16) were transplanted. The median time between surgeries amounted to 19.9 months (IQR: 7.3–32.9), and the median waiting list time was 4.4 months (IQR: 1.6–10.3).

The LT group accounted for 222 patients first treated with LT, two of whom received a liver graft from a deceased after-cardiac death donor; the remaining 220 were transplanted with a deceased after-brain death donor liver graft. Out of 222 patients, 177 (80%) were men, and 47 (20%) were women; the median age at the time of transplantation was 59 years (IQR: 53–64) (Table 1). The number of Child–Pugh class A patients amounted to 81 (36%), those in class B to 115 (52%), and those in class C to 26 (12%); the median clinical MELD-Na score was 13 (IQR: 10–17) at the time of the LT. On imaging techniques, 130 patients (59%) had monofocal HCC, 52 patients (23%) had bifocal HCC, and 40 patients (18%) had up to three HCC nodules. Native livers were histologically graded as well to moderately differentiated in 132 patients (59%); the remaining 93 (41%) had poorly differentiated HCC. Tumor sizes were histologically classified (pT) as T1 in 90 cases (41%), T2 in 123 cases (55%), and T3 in the remaining nine (4%). The microvascular invasion was found in 43 patients (19%). During the study period, the Italian mean rate of the deceased donation was 21.2 ± 1.8 donors per million inhabitants per year. In contrast, in our region, the mean rate was 10.5 ± 3.2 donors per million per year. In most cases, cirrhosis was secondary to chronic viral infection (66%); in particular, to hepatitis C virus (HCV)-related liver cirrhosis ($n = 117$, 53%), hepatitis B virus (HBV)-related liver cirrhosis ($n = 29$, 13%), alcohol-related liver cirrhosis ($n = 30$, 13%), nonalcoholic fatty liver disease (NASH) ($n = 42$, 19%), and others ($n = 4$, 1.8%).

Of note, over the years, there has been an increase in cases of HCC arising from post-NASH cirrhosis (Figure 2). The distribution of waiting list times was highly positively skewed with a median of 2.0 months, an IQR of 0.7–6.1, and a range from 0.2 to 133 months. One patient underwent a liver resection

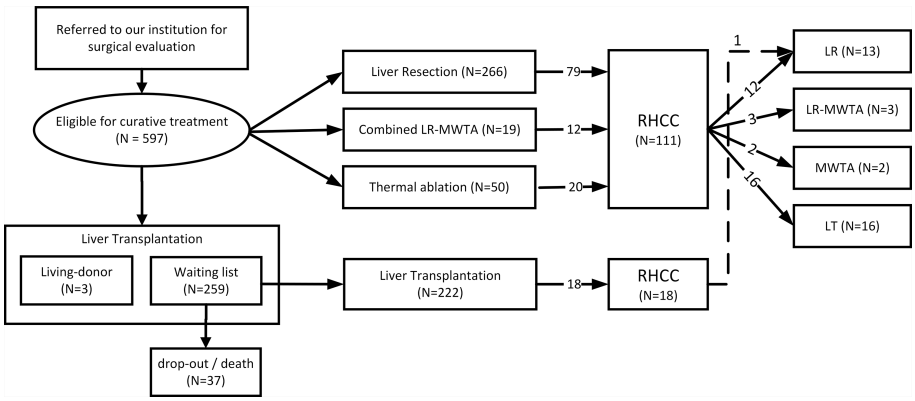

FIGURE 1
Patient and treatment selection flowchart.

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TABLE 1 Clinical and demographic characteristics of 557 patients affected by hepatocellular carcinoma who underwent surgical treatment.

	Liver resection/ablation	Liver transplantation	Overall
N	**335**	**222**	**557**
Male sex (no. (%))	255 (76)	177 (80)	432 (78)
Age ((years), median [IQR])	68 [61, 73]	59 [53, 64]	
Etiology of liver disease (no. (%))			
Hepatitis C virus-related liver cirrhosis	216 (64)	117 (53)	333 (60)
Hepatitis B virus-related liver cirrhosis	32 (9)	29 (13)	61 (11)
Alcohol-related liver cirrhosis	15 (5)	30 (13)	45 (8)
Nonalcoholic fatty liver disease	59 (18)	42 (19)	101 (18)
Cryptogenic cirrhosis	2 (0.6)	1 (0.5)	3 (0.5)
Noncirrhotic liver	9 (3)	0 (0)	9 (2)
Cholestatic liver disease	2 (0.6)	3 (1.4)	5 (0.9)
Number of HCC lesions (no. (%))			
1	253 (76)	130 (59)	383 (69)
2	63 (19)	52 (23)	115 (21)
3	19 (6)	40 (18)	59 (11)
Maximum tumor size (median [IQR])	3.0 [1.8, 4.6]	2.2 [1.5, 3.2]	2.5 [1.7, 4.0]
Histological size of the tumor (pT)			
T1	162 (48)	90 (41)	252 (45)
T2	127 (38)	123 (55)	250 (45)
T3/T4	46 (14)	9 (4)	55 (10)
Bilirubin ((mg/dl), median [IQR])	0.6 [0.4, 0.9]	1.5 [0.8, 3.0]	0.8 [0.5, 1.4]
INR (median [IQR])	1.1 [1.0, 1.1]	1.2 [1.1, 1.4]	1.1 [1.0, 1.2]
Platelet count ((×10^9/L), median [IQR])	156 [111, 215]	75 [51, 98]	117 [75, 180]
Creatinine ((mg/dl), median [IQR])	0.9 [0.8, 1.1]	0.8 [0.7, 1.1]	0.9 [0.8, 1.1]
Child–Pugh score			
A5	240 (72)	33 (15)	273 (49)
A6	75 (22)	48 (22)	123 (22)
B7	8 (2)	50 (23)	58 (10)
B8	2 (1)	28 (13)	30 (5)
B9	10 (3)	37 (16)	47 (8)
C10	0 (0)	22 (10)	22 (4)
C11	0 (0)	4 (2)	4 (0.7)
MELD-Na (median [IQR])	9 [8, 10]	13 [10, 17]	10 [8, 13]
Histological grading			
G1	63 (19)	56 (25)	119 (21)
G2	154 (46)	76 (34)	230 (41)
G3	97 (29)	89 (40)	186 (33)
G4	21 (6)	4 (2)	25 (4)
Vascular invasion (no. (%))	112 (33)	43 (19)	155 (28)
First treatment			
Liver resection (LR)	266 (79)	–	266 (48)
Microwave thermal ablation (MWTA)	50 (15)	–	50 (9)
Combined LR/MWTA	19 (6)	–	19 (3)
Liver transplantation (LT)	–	222 (100)	222 (40)
Minimally invasive approach (no. (%))	176 (53)	0 (0)	176 (32)
Second treatment	**33 (10)**	**1 (0.5)**	**34 (6)**
LR	12 (3.6)	1 (0.5)	13 (2)
MWTA	2 (0.6)	0 (0)	2 (0.4)

(Continued)

TABLE 1 Continued

	Liver resection/ablation	Liver transplantation	Overall
Combined LR/MWTA	3 (0.9)	0 (0)	3 (0.5)
OLT	16 (4.7)	0 (0)	16 (3)
Months between first and second treatment [median (IQR)]	19.9 (7.3–32.9)	0.5 (0.3, 34.7)	19.9 [7.0, 33.9]

The bold values provided information about second treatments, and the following surgical options are the specific treatments:
LR
MWTA
Combined LR/MWTA
OLT.

due to RHCC 5.7 years after the transplant, and two other patients underwent second liver transplantation due to graft nonfunction (not to RHCC).

Recurrence of hepatocellular carcinoma

The RHCC was markedly higher for patients treated with LR/LRT than for those treated with LT. Overall, 111 patients experienced tumor recurrence in the LR/MWTA group, instead of only 18 transplanted patients. In detail, RHCCs after LT were developed in 18 (8%) out of 222 recipients, of which two patients had only intrahepatic HCC recurrences and the other 16 developed metastases (eight in the lungs, three in the bone, two in the adrenal gland, one in the brain, and two involved multiple extrahepatic systems). After 1, 3, and 5 years from treatment, the estimated recurrence rates for patients in the LR/MWTA group were 32% (95% CI: 24–38), 72% (95% CI: 62–79), and 94% (95% CI: 83–98), respectively, compared to 5% (95% CI: 2–8), 8% (95% CI: 4–12), and 9% (95% CI: 5–14) for patients in the LT groups (Figure 3; Table 2).

Considering the hazard rates (HRs) of the two groups were nonproportional, a univariate Cox model for time to RHCC was fitted in a stratified manner. Within the LR/MWTA group, significantly associated with tumor recurrence were hepatitis B virus infection (which has a protective role with HR: 0.34, 95% CI: 0.13–0.94, $p = 0.038$), number of HCC nodules (HR: 1.54, 95% CI: 1.22–1.94, $p < 0.001$), size of the largest nodule (HR: 1.06, 95% CI: 1.01–1.12, $p = 0.023$), serum bilirubin (HR: 1.57, 95% CI: 1.03–2.40, $p = 0.038$), and international normalized ratio (HR: 16.40, 95% CI: 2.30–118.0, $p = 0.006$). For transplanted patients, the only significant risk factor in univariate analysis was the number of HCC nodules (HR: 1.61, 95% CI: 1.05–2.47, $p = 0.030$) (Table 3).

Among the 111 patients with RHCC in the first group, 33 were iteratively treated with further curative treatment (12 were treated with LR, two with MWTA, three with a combined LR-MWTA treatment, and 16 underwent LT). Only one of the 18 recurrent patients previously treated with LT underwent LR (Figure 1). For these patients who were eligible for liver transplantation as the secondary HCC treatment, 1-, 2-, and 3-year survival were, respectively, 7% (95% CI: 0–19), 7% (95% CI:

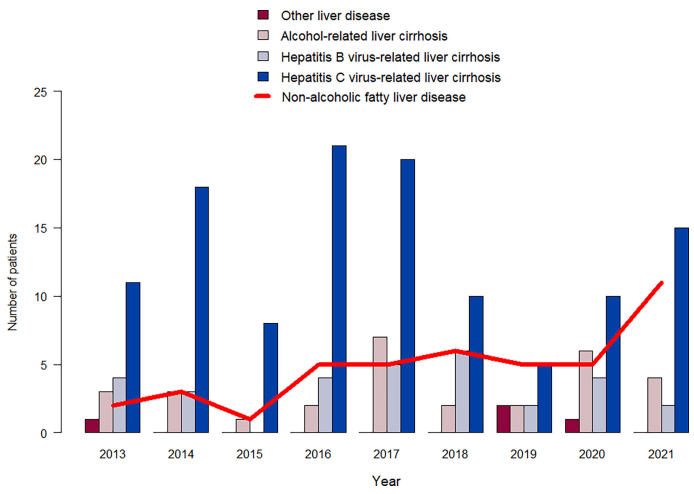

FIGURE 2
Distribution of different etiologies of liver disease by year of transplantation.

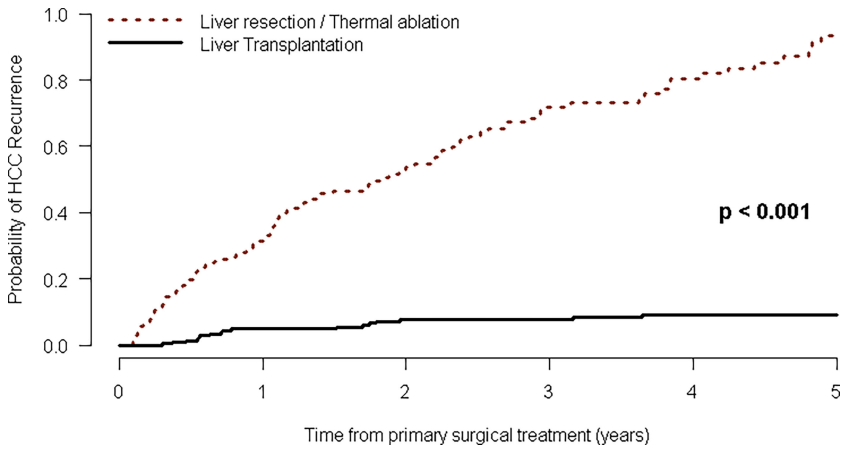

FIGURE 3
Kaplan–Meier curves of time to HCC recurrence after first-line curative treatment.

0–19), and 17% (95% CI: 0–37), as opposed to those who were treated with LR/MWTA after a previous surgical treatment, whose survival estimates amounted to 37% (95% CI: 4–58), 62% (95% CI: 13–83), and 87% (95% CI: 23–99) at 1, 2, and 3 years, respectively (Table 4), thus showing a marked although nonstatistically significant survival experience (log-rank test $p < 0.001$, Figure 4).

Uni- and multivariable Cox models were fitted to investigate the risk factors for further RHCC in every 34 patients who were treated with secondary IDLS. In univariate analysis, patient age was found to be a predictor of RHCC in the posttreatment setting (HR: 1.09, 95% CI: 1.01–1.17, $p = 0.029$), instead of the protective roles of LT for the treatment of RHCC after primary IDLS (HR: 0.08, 95% CI: 0.02–0.37, $p = 0.002$), and the impact of previous minimally invasive treatment (HR: 0.24, 95% CI: 0.08–0.76, $p = 0.015$). At multivariable analysis, the best Akaike Information Criterion (AIC) forward stepwise variable selection algorithm confirmed the protective roles of LT for primary RHCC after IDLS (HR: 0.06, 95% CI: 0.01–0.36, $p = 0.002$), of the time relapsed between the first and second IDLS treatments (HR: 0.97, 95% CI: 0.94–0.99, $p = 0.044$), and the impact of previous minimally invasive treatment (HR: 0.28, 95% CI: 0.08–1.00, $p = 0.051$) as the best set of predictors of RHCC, respectively (Table 5).

There were 64 deaths (27%) during follow-up. Causes of death were attributable to RHCC in 17 patients (27% of deaths); septic shock and multiorgan failure in 23 patients (36%); liver disease recurrence in three patients (5%); the onset of other (non-HCC) neoplasms in four patients (6%); surgical complication or graft nonfunction in three patients (5%); and the remaining 14 (22% of all dead patients) are attributable to other causes, such as cardiac arrest, cerebral hemorrhage, and fulminant meningitis–encephalitis. Overall survival estimates at 1, 3, and 5 years after LT were, respectively, 87% (95% CI: 83–91), 73% (95% CI: 68–80), and 68% (95% CI: 62–75).

Discussion

The non-HCC field for hepato-pancreato-biliary surgeons has expanded in both scope and surgical indications (31, 32). There are different treatment options for HCC concerning liver function and the type of tumor. The EASL-EORTC guidelines recommend hepatectomy for HCC patients at BCLC stage 0 or

TABLE 2 Hepatocellular carcinoma recurrence rate of 557 patients who underwent surgical treatment.

Time	Liver resection/ablation			Liver transplantation		
	Events	Kaplan–Meier estimate	(95% CI)	Events	Kaplan–Meier estimate	(95% CI)
1 year	55	32%	(24–38)	10	5%	(2–8)
2 years	81	54%	(44–62)	15	8%	(4–12)
3 years	98	72%	(62–79)	15	8%	(4–12)
4 years	104	80%	(70–87)	17	9%	(5–14)
5 years	111	94%	(83–98)	17	9%	(5–14)

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TABLE 3 Cox models for time to hepatocellular carcinoma recurrence after first-line curative treatment.

	Liver resection/thermal ablation			Liver transplantation		
	HR	95% CI	*p*	HR	95% CI	*p*
Male sex	0.94	0.59–1.49	0.802	1.35	0.39–4.66	0.637
Patient's age	0.99	0.98–1.01	0.468	1.03	0.96–1.10	0.457
Alcohol usage	1.78	0.64–4.92	0.266	0.38	0.05–2.87	0.349
Hepatitis C virus infection	1.40	0.89–2.22	0.148	1.04	0.41–2.63	0.94
Hepatitis B virus infection	**0.34**	**0.13–0.94**	**0.038**	1.84	0.60–5.59	0.283
Nonalcoholic fatty liver disease	0.57	0.28–1.18	0.129	0.59	0.14–2.58	0.487
Number of HCC nodules	**1.54**	**1.22–1.94**	**<0.001**	**1.61**	**1.05–2.47**	**0.030**
Size of the largest nodule	**1.06**	**1.01–1.12**	**0.023**	1.36	0.98–1.88	0.064
Serum bilirubin	**1.57**	**1.03–2.40**	**0.038**	0.94	0.75–1.17	0.56
International normalized ratio	**16.40**	**2.30–118.0**	**0.006**	0.33	0.03–3.36	0.349
Serum creatinine	0.84	0.55–1.28	0.424	0.89	0.35–2.26	0.813
Serum sodium	1.01	0.94–1.08	0.817	1.06	0.93–1.20	0.389
Model for end-stage liver disease	1.03	0.96–1.10	0.384	0.95	0.86–1.05	0.349
Platelets count	1.00	1.00–1.00	0.939	1.00	1.00–1.01	0.25
Microvascular invasion	1.26	0.81–1.96	0.306	0.76	0.08–7.45	0.812
Histological grade ≥3	1.53	0.99–2.36	0.057	1.27	0.18–9.01	0.812
Waiting list time				0.89	0.76–1.05	0.17
Donor age				1.02	0.99–1.05	0.27

The bold values provided information about second treatments, and the following surgical options are the specific treatments:
LR
MWTA
Combined LR/MWTA
OLT.

BCLC-A with no portal hypertension (PHT) (4). Indication for surgery also depends on the number of nodules, the diameter of tumors, vascular invasion, and extrahepatic disease. In the 2016 EASL updated guidelines, liver resection was also introduced as a possible treatment for patients with PHT by endorsing a risk algorithm for postoperative liver decompensation. This algorithm included the MELD score, the presence of PHT, and type of resection (6).

A recent multicentric study showed that cirrhotic patients with a hepatic venous pressure gradient of ten or more could undergo liver resection with an acceptable 90-day perioperative mortality and morbidity (6% and 27%, respectively) and persistent liver decompensation (10% at 3 months) (7). In many Asian studies, the extent of surgery was applied where technically feasible, including in patients with macrovascular invasion (33, 34). In 2016, a study conducted on 6,474 patients affected by HCC and macrovascular invasion compared surgical vs. nonsurgical treatment demonstrated a median and 5-year survival of 29.4 months and 32.9% in the resected patients versus 18.8 months and 20.1% in patients treated nonoperatively (35).

Nevertheless, for successful outcomes after LRT, LT represents the only valid treatment for both malignancy and underlying cirrhosis. Among our transplanted patients within the Milan criteria, the HCC recurrence rate is about 9%, confirming data existing in the literature (36, 37).

In this study, the maximum nodule size, number of nodules, serum bilirubin, and international normalized ratio represent risk factors for RHCC after LRT. In the same way, some studies

TABLE 4 Hepatocellular carcinoma recurrence rate of 34 patients who underwent a second surgical treatment.

Time	Liver resection/ablation			Liver transplantation		
	Events	Kaplan–Meier estimate	(95% CI)	Events	Kaplan–Meier estimate	(95% CI)
1 year	5	37%	(4–58)	1	7%	(0–19)
2 years	7	62%	(13–83)	1	7%	(0–19)
3 years	9	87%	(23–99)	2	17%	(0–37)

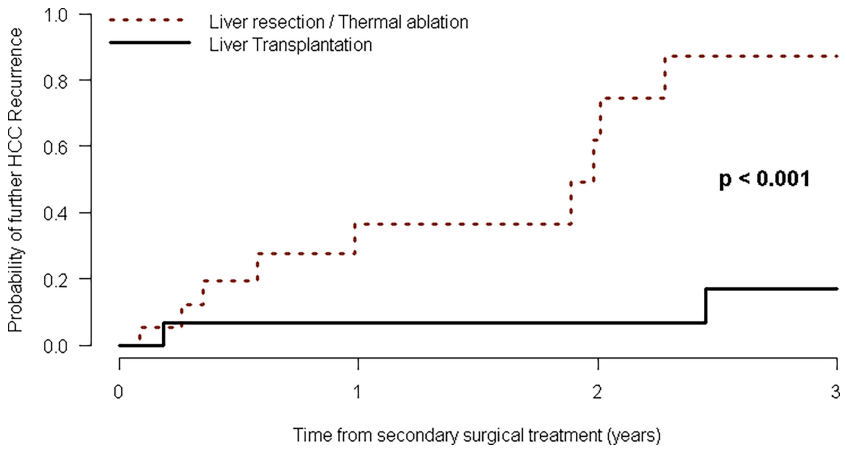

FIGURE 4
Kaplan–Meier curves of time to HCC recurrence after second-line curative treatment.

in the literature have also demonstrated the role of end-stage liver disease in RHCC. In this setting, precise scores, such as the Model of Recurrence After Liver transplant score, have yet to provide a specific tool for predicting RHCC and risk stratification pre- and postoperatively (38).

Several studies have focused their interest on finding the best model to predict post-LT HCC recurrence. Firstly, the Milan criteria in 1996 included tumor burden and the number of nodules at explant (11). In 2012, a multicentre French study incorporated an AFP threshold, the number of nodules, and the largest tumor diameter into a prognostic score (36). In our multivariate analysis, we confirmed the prognostic role of and a number of nodules, and these data are widely validated in the literature; the RETREAT score showed elevated AFP, the presence of microvascular invasion on the explant, and the largest viable tumor diameter plus the number of viable tumors on the explant, as possible prognostic factors (37).

However, in cases of patients beyond the Milan criteria, the recent XXL trial showed that effective downstaging treatment correlates significantly with a higher tumor event-free survival after LT ($p = 0.003$) (10, 39, 40). The United Network of Organ Sharing (UNOS) guidelines suggest a downstaging protocol for patients beyond MC, focusing on their response to bridge therapy (41). Also, a recent study demonstrated that disease progression after bridging therapy is an independent risk factor for recurrence and mortality (42).

Another relevant data emerging from our multivariate analysis is the "protective role" of the minimally invasive approach. If patients develop RHCC much more time after the first IDLS, it is possible to experience longer tumor-free survival even after subsequent surgical treatments (42–46). The clinical entity of RHCC can be developed in different settings, and it depends on which first-line therapy was chosen. There is little information in the literature about this type of patient because those who underwent an intentional curative surgical treatment are not initially evaluated for liver transplantation. These data also strengthen the importance of tumor behavior and surveillance for this group of patients.

Recently, in the first prospective, randomized, controlled trial, there has been evidence of longer patient survival and fewer tumor events after LT in patients who achieved success and sustained downstaging of HCCs exceeding the Milan criteria, compared with those in the nontransplantation therapy group (10). In this retrospective study, we showed the protective roles of LT for primary RHCC after IDLS and of the time relapsed between the first and second IDLS treatments for patients affected by HCC with

TABLE 5 Cox models for time to hepatocellular carcinoma recurrence after second-line curative treatment.

	Univariable Cox models			Multivariable Cox model		
	HR	95% CI	*p*	HR	95% CI	*p*
Male sex	0.50	0.13–1.95	0.319			
Patient's age	1.09	1.01–1.17	0.029			
Liver transplantation after first IDLS	0.08	0.02–0.37	0.002	0.06	0.01–0.36	0.002
Time from the first treatment	0.98	0.94–1.02	0.27	0.97	0.94–0.99	0.044
Previous minimally invasive treatment	0.24	0.08–0.76	0.015	0.28	0.08–1.00	0.051

more advanced liver disease and higher bilirubin levels. In this setting, the impact of previous minimally invasive treatment could lead to lower rates of HCC recurrence and peritoneal adhesions On the other hand, this study has different limitations: the retrospective design, the inclusion only of patients within MC, and the selection of patients referred to a liver transplant center.

For our transplant center, considering the low rate of deceased donation, we can suggest that IDLS represents the best option for patients affected by HCC and fit for surgery, but these results confirm the importance of starting the evaluation for LT both for recurrence and mortality.

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 ISMETT Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: DP, MB, DC, FF, SL, and SG. Made substantial contributions to data interpretation: PB, SC, GD, CC, MC, and SG. Performed data acquisition, as well as providing administrative, technical, and material support: DP, SK, BM, and SG. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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
Alessandro Vitale,
University Hospital of Padua, Italy

REVIEWED BY
Francesca Marcon,
IRCCS Ca 'Granda Foundation Maggiore Policlinico Hospital, Italy
Marcello Di Martino,
Princess University Hospital, Spain
Federico Mocchegiani,
Marche Polytechnic University, Italy
Roberto Montalti,
Federico II University Hospital, Italy

*CORRESPONDENCE
Hong Wu
407723080@qq.com

†These authors have contributed equally to this work

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Laparoscopic repeat hepatectomy versus conventional open repeat hepatectomy for recurrent hepatocellular carcinoma: A systematic review and meta-analysis

Fulong Hao[1,2†], Hancong Li[3†], Nan Li[4,5†], Jiaxin Li[1] and Hong Wu[1*]

[1]Department of Liver Surgery and Liver Transplantation Centre, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Hepatobiliary Surgery, Suining First People's Hospital, Suining, China, [3]West China School of Medicine, West China Hospital, Sichuan University, Chengdu, China, [4]Engineering Research Centre of Medical Information Technology, Ministry of Education, West China Hospital, Sichuan University, Chengdu, China, [5]Information Technology Centre, West China Hospital of Sichuan University, Chengdu, China

Background: Repeat hepatectomy has been proven to be an effective treatment in patients with recurrent hepatocellular carcinoma (RHCC). However, for RHCC, it is still controversial whether laparoscopic hepatectomy is superior to conventional ones. The present meta-analysis was carried out to investigate the safety and overall effect of laparoscopic repeat hepatectomy (LRH) to open repeat hepatectomy (ORH) for patients with RHCC.

Methods: A meta-analysis was registered at PROSPERO, and the registration number is CRD42021257569. PubMed, Web of Science, and EMBASE were searched based on a defined search strategy to identify eligible studies before 25 April 2022. Data on operative times, bleeding volume, overall complications, 90-day mortality, blood transfusion, length of stay, overall survival rate, and long-term recurrence-free survival rate were subjected to meta-analysis.

Results: Overall, we identified nine studies of LRH versus ORH enrolling a total of 945 patients (460 and 485 underwent LRH and ORH, respectively). The present meta-analysis revealed non-significant differences in operative time, blood transfusion, overall complications, 90-day mortality, 3-year overall survival rate, 5-year overall survival rate, and long-term recurrence-free survival rate

between the two groups. Alternatively, comparing LRH with ORH, LRH has less bleeding volume ($p < 0.001$) and a shorter length of stay ($p = 0.005$).

Conclusion: LRH is a feasible and effective treatment strategy for RHCC.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/#searchadvanced, identifier CRD42021257569.

KEYWORDS

recurrence, hepatocellular carcinoma, laparoscopic repeat hepatectomy, open repeat hepatectomy, meta-analysis

1 Introduction

Liver cancer is the third leading cause of cancer-related death worldwide and ranks sixth in terms of morbidity (1). Hepatocellular carcinoma (HCC) accounts for 75% to 95% of all primary liver cancers (2). Due to its rising incidence and unfavorable prognosis, HCC was considered a major global health problem (3). Hepatectomy has long been the frequent curative treatment for HCC and is especially appropriate for patients at an early stage (4–6). Unfortunately, tumor recurrence occurred in as many as 60%–80% of cases at 5 years, which made the long-term outcomes of HCC to remain unsatisfactory (6–9). No accepted neoadjuvant or adjuvant therapies have been confirmed to reduce the risk of recurrence (6, 7, 10). Hence, an effective therapeutic regimen for recurrence is essential to prolonging survival for HCC patients (11, 12).

Currently, varieties of remedies including repeated hepatectomy, liver transplantation, embolization, ablation, and molecular targeted therapy have been widely used in the clinical treatment of recurrent hepatocellular carcinoma (RHCC) (11, 13, 14). However, guidelines for the management of RHCC remained controversial (11, 12). Multiple studies have endorsed repeat hepatectomy as an effective treatment with favorable long-term surgical outcomes for RHCC in the past few decades (15–17).

Previous operation history had been among the contraindications for laparoscopic surgery (18). Nevertheless, with the improvement of laparoscopic instruments and accumulation of surgical techniques, laparoscopic hepatectomy (LH) has emerged as a viable alternative treatment to open hepatectomy (OH) and has been applied in specific RHCC patients safely (19, 20). Previous literature has confirmed the safety and efficiency of LH, emphasizing that LH was superior to OH due to less bleeding volume, shorter operation time, and faster recovery (21, 22).

However, postoperative adhesions as well as changes in anatomical land marks and liver deformation may cause technical challenges for laparoscopic repeat hepatectomy (LRH). The indication criteria for LRH have yet to be clearly defined (23). Hence, whether LRH or ORH is the preferred treatment for RHCC remains elusive.

To address this issue, we conducted a meta-analysis to compare the clinical efficacy and safety of LRH and ORH for patients with RHCC.

2 Methods

This study was carried out following the PRISMA 2020 guideline (24). The protocol of the present review was registered and allocated the identification number CRD42021257569 in the PROSPERO database.

2.1 Search strategy and study selection

Published documents before 25 April 2022 were retrieved using the electronic databases PubMed, EMBASE, Web of Science, and Cochrane Central Register, by two independent researchers (FL Hao, HC Li). The following subject terms were employed in the literature search: recurrent liver cancer, recurrent hepatocellular carcinoma, laparoscopic hepatectomy, open hepatectomy, liver resection, and minimally invasive surgery. Supplementary Table S1 shows our search strategy. For gaining additional trials, a manual search of eligible studies in references was complemented.

2.2 Inclusion and exclusion criteria

Two researchers (FL Hao, HC Li) identified and reviewed full-text articles that were regarded as relevant by screening the titles and abstracts. Disagreements were resolved by a team discussion.

Inclusion criteria were as follows (1): participants—patients with RHCC after initial curative liver resection (2); types of

interventions—LRH and ORH (3); data available on interesting surgical outcomes.

Exclusion criteria were as follows (1): The publication type was observational clinical studies, case–control studies, abstracts, editorials, case reports, letters, and expert opinion (2); studies without available data, non-English or experimental studies.

2.3 Data extraction

Two researchers (FL Hao, HC Li) independently extracted relevant data with a standardized form. The data from studies based on a PSM analysis were extracted from the post-PSM analysis. Any ambiguity was discussed with the third researcher (N Li).

Based on the predetermined criteria, the following data were extracted: name of the first author, publication year, study design, country, number of patients, mean age, gender, tumor size, tumor number, operative times, bleeding volume, blood transfusion, number of patients converted from laparoscopy to laparotomy, overall complication, hospitalization, 90-day mortality, 1-, 3-, and 5-year survival (OS) rate, and 1-, 3-, and 5-year recurrence-free survival (RFS) rate.

2.4 Quality assessment

The Newcastle–Ottawa Scale (NOS) developed for evaluating the quality of eligible studies was utilized by two independent reviewers (FL Hao, HC Li) (24). NOS score ≥6 was defined as high-quality. Any disagreements were discussed and resolved through consensus.

2.5 Statistical analysis

Statistical analysis was performed using the Review Manager software (RevMan V.5.3.4). Continuous data were expressed as 95% confidence interval (CI) and mean difference (MD), while dichotomous data used odds ratio (OR). For overall survival data, we used Engauge Digitizer (RevMan V.4.1) to extract OS and RFS data from survival curves (25). Using the method originally described by Hozo et al., medians with ranges were converted into means with standard deviations (26). Publication bias was assessed *via* Begg's funnel plot and Egger's linear regression test. Heterogeneity was examined by the I^2 statistic. Statistical heterogeneity is significant when I^2 ≥50%, and the random-effect model (REM) is utilized; if not (I^2 <50%), the fixed-effect model (FEM) is applied.

3 Results

3.1 Literature search results

The literature search yielded 1,651 relevant English publications which were considered potential studies. Eight hundred twenty-five of them were duplicates. Seven hundred ninety articles were excluded for irrelevance to the objective after screening the abstract and partial full text. Thirty-six full-text articles met the eligibility for assessment. Through reading the full text, 27 studies were excluded due to inappropriate study design or content. Finally, according to the inclusion criteria, nine studies (23, 27–34) of a total of 945 patients (460 and 485 underwent LRH and ORH, respectively) were found to be eligible for the present meta-analysis. Figure 1 shows the procedure of study selection in a flow diagram. Detailed NOS scores are presented in Supplementary Table S2.

3.2 Characteristics of the included studies

In this review, we included nine studies involving 945 patients. The overall characteristics of the included articles are shown in Table 1. The sample sizes varied from 33 to 476, and most study designs were PSM studies.

3.3 Operative outcomes

3.3.1 Operative time

All of the nine included studies made a comparative evaluation of operative times. Our analysis showed that the operative time in LRH patients was not inferior to those of ORH (MD: 11.63 min; 95% CI: -17.58 to 40.83; p = 0.44). Heterogeneity was high (I^2 = 79%) and analyzed in the REM (Figure 2A).

3.3.2 Bleeding volume

Nine studies that comprised 945 patients (460 and 485 underwent LRH and ORH, respectively) had reported the bleeding volume. Compared with the ORH group, the bleeding volume was lesser in the LRH group (MD: -237.23 ml; 95% CI: -338.26 to -136.20; p<0.00001). Heterogeneity was high (I^2 = 90%) and analyzed in the REM (Figure 2B). A summary of meta-analysis results can be found in Table 2.

3.3.3 Blood transfusion

Blood transfusion data were available in six studies (23, 27–30, 32). There was no statistical difference in blood transfusion between the two groups (OR: 0.31; 95% CI:0.06 to 1.63; p = 0.17), indicating that LRH and ORH had similar effects on this item. Heterogeneity was high (I^2 = 69%) and analyzed in the REM (Figure 2C).

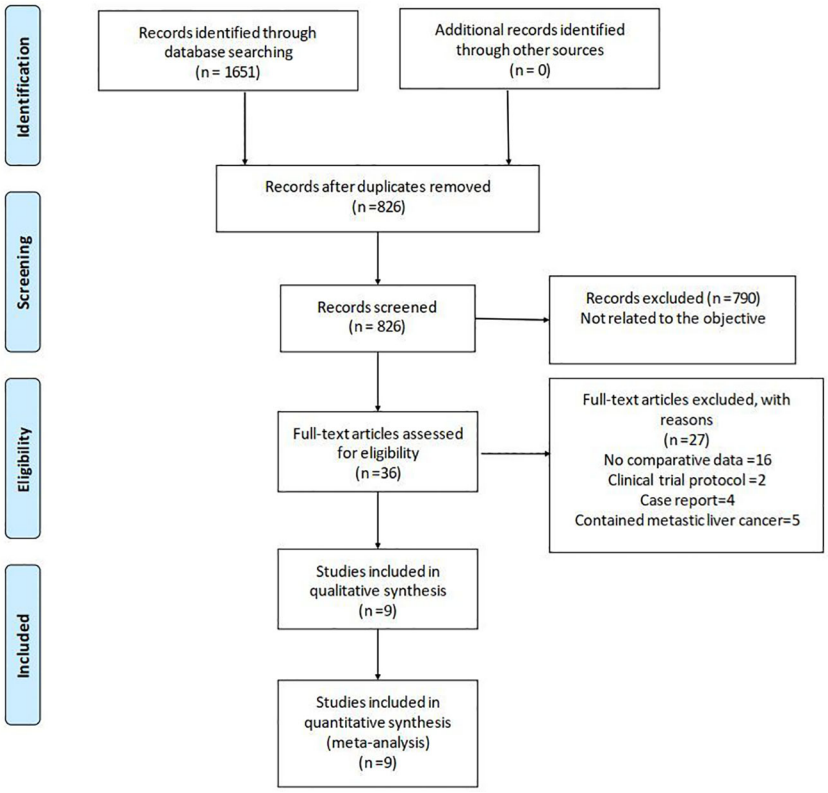

FIGURE 1
Flowchart of study identification and selection.

3.4 Postoperative outcomes

3.4.1 Overall complication rates

Eight studies (23, 27–33) with a total of 881 patients (429 and 452 underwent LRH and ORH, respectively) mentioned the overall complications, and the result of a comprehensive analysis showed that LRH was associated with a similar overall complication rate for ORH (OR: 0.44; 95% CI: 0.17 to 1.14; p = 0.09). The heterogeneity was high (I^2 = 64%) and analyzed in the REM (Figure 3A).

3.4.2 Length of stay

All these nine studies had reported hospitalization time. Noticeably, the meta-analysis certified that RHCC treated with LRH presented shorter hospital stay compared with the ORH group (MD = -2.52; 95% CI: -4.27 to -0.76; p = 0.005), with high heterogeneity (I^2 = 86%) in the REM (Figure 3B).

3.4.3 90-Day mortality

Of the nine studies, four trials (27–29, 32) performed an objective evaluation of the 90-day mortality. The result of the present study considered no difference in 90-day mortality between LRH and ORH groups (OR = 1.00; 95% CI: 0.25 to 4.06; p = 1.00), with low heterogeneity (I^2 = 0%) in the FEM (Figure 3C).

3.5 Oncological outcomes

3.5.1 Overall survival

Only three studies (27, 29, 31) assessed 1-year overall survival rate, and the result of our meta-analysis demonstrated that the 1-year survival rates for LRH were lower than those for ORH (OR: 0.60; 95% CI: 0.41 to 0.89; p = 0.01), into with moderate heterogeneity (I^2 = 20%) in the REM (Figure 4A). Two studies (27, 29) compared the 3-year overall survival rates, and our results revealed no difference in 3-year overall survival rate (OR: 1.06; 95% CI: 0.31 to 3.62; p = 0.93), with high heterogeneity (I^2 = 70%) in the REM (Figure 4B). Two studies (27, 29) assessed the 5-year overall survival rate; similarly, LRH had a proximate 5-year overall survival rate compared with the ORH group (OR: 0.76; 95% CI: 0.44 to 1.32; p = 0.33), with moderate heterogeneity (I^2 = 31%) in the FEM (Figure 4C).

TABLE 1 The main characteristics of the included studies in this meta-analysis.

Author year	Country	Study design	Period	Patients		Age (year)		Gender (M/F)		Tumor size (cm)		Pathology	No. of tumors		No. of conversion	Child-Pugh Score (A/B)		Previous operation (open/LH)		Etiology		BCLC stage		Tumor grading		Tumor location		Co-morbid illness		Resection margin	
				LH (n)	OH (n)	LH	OH	LH	OH	LH	OH		LH	OH		LH	OH	LH	OH	LH	OH	LH	OH	LH	OH	LH	OH	LH	OH	LH	OH
Kanazawa-2013	Japan	RM	2006-2011	20	20	70 (46–83)	65 (43–74)	19/1	15/5	1.7 (0.7–3.5)	2.2 (1.3–4.1)	HCC	Solitary: 16Multiple:4	Solitary: 18Multiple:2	2	19/1	17/3	15/5	NA	HBV:4HCV:11NBNC:5	HBV:6HCV:10NBNC:4	NA	NA	NA	NA	Segments II, III, IV, V, VI: 13Segments VII, VIII:5Segments I:1Biober:1	Segments II, III, IV, V, VI: 13Segments VII, VIII: 4Segments I:2Biober:1	NA	NA	NA	NA	NA	NA
Chan-2014	China	Case-match	2004-2013	11	22	61(43-80)	62(43-76)	8/3	16/6	2 (1.0–4.5)	2 (1.0–5.0)	HCC	Solitary: 10Multiple:1	Solitary: 20Multiple:2	0	11/0	22/0	6/5	NA	HBV:7HCV:1	HBV:18HCV:2	NA	NA	NA	NA	Left lobe: 7Right lobe: 4	Left lobe: 14Right lobe: 8	Cardiovascular: 3Respiratory: 1	Cardiovascular: 6Respiratory:1Diabetes mellitus: 2Gastrointestinal: 2	Not involved: 11Involved: 0	Not involved: 20Involved: 2
Zhang-2016	China	P	2014-2014	31	33	54 (37–66)	59.5 (34–65)	26/5	27/6	2.5 ± 1.0	3.8 ± 1.1	HCC	NA	NA	0	31/0	33/0	31/0	33/0	NA	NA	NA	NA	NA	NA	Left lobe: 15Right lobe: 16	Left lobe: 14Right lobe: 19	NA	NA	2.1 ± 1.2	2.2 ± 0.6
Liu-2017	China	PSM	2008-2015	30	30	56.5 (27–79)	48.5 (28–79)	23/7	28/2	2.1 (1.0–5.0)	2.45 (1.0–4.3)	HCC	Solitary: 25Multiple:5	Solitary: 28Multiple:2	4	30/0	27/3	21/9	NA	HBV:29	HBV:29	NA	NA	NA	NA	Segments II, III, IVa, V, VI:18Segments IVb, VII, VIII:4Segments I:1Biober:7	Segments II, III, IVa, V, VI:15Segments IVb, VII, VIII:8Segments I:3Biober:4	Bile leak: 1Intra-abdominal hemorrhage:1Abdominal infection: 0Ascites:0Liver failure 0	Bile leak: 3Intra-abdominal hemorrhage:1Abdominal infection: 4Ascites:1Liver failure 1	Involved:30	Involved:30
Goh-2018	Singapore	PSM	2015-2017	20	20	68.5 (67.0–71.75)	69 (63.0–72.25)	18/2	18/2	2 (1.15–2.78)	2.6 (1.5–3.0)	HCC	Solitary: 19Multiple:1	Solitary: 18Multiple:2	3	NA	NA	7/13	NA	HBV: 10	HBV: 10	NA	NA	NA	NA	NA	NA	NA	NA	Resection margin <1 mm: 1	Resection margin <1 mm: 3
Onoe-2019	Japan	R	2007-2018	30	42	70.9 (50–85)	72.0 (59–88)	23/7	30/12	1.25 (0.08–3.5)	1.75 (0.5–6.0)	HCC	1 (1-3)	1 (1-4)	2	30/0	34/8	21/9	36/6	HBV: 10HCV: 14NBNC: 6	HBV: 13HCV: 17NBNC: 12	NA	NA	NA	NA	Segments VII, VIII: 12Others: 18	Segments VII, VIII: 15Others: 27	NA	NA	NA	NA
Morise-2020	Japan	PSM	2007-2017	238	238	67.1 ± 11.8	66.4 ± 10.2	181/57	184/54	2.75 ± 2.88	2.77 ± 2.64	HCC	1.28	1.32	NA	NA	NA	181/57	187/51	NA	NA	NA	NA	NA	NA	Anterolateral: 171Posterosuperior:67	Anterolateral: 181Posterosuperior: 57	Ascites: 238Encephalopathy: 238Varices: 238	Ascites: 238Encephalopathy: 238Varices: 238	NA	NA
Gon-2020	Japan	PSM	2008-2019	23	23	72 (67–79)	72 (67–79)	18/5	18/5	1.9 (1.2–2.5)	2.0 (1.3–2.6)	HCC	Solitary: 22Multiple:1	Solitary: 23Multiple:0	2	23/0	23/0	21/2	23/0	HBV/HCV: 15NBNC: 8	HBV/HCV: 21NBNC: 2	NA	NA	NA	NA	Segments I, VII, VIII: 8Segments II-VI: 15	Segments I, VII, VIII: 9Segments II-VI: 14	NA	NA	NA	NA
Chen-2021	China	PSM	2017-2018	57	57	56 (36-78)	59 (34-77)	49/8	50/17	1.5 (0.6-4.5)	1.7 (0.8-4.5)	HCC	1 (1-4)	1 (1-2)	6	57/0	57/0	50/7	52/5	HBV: 52	HBV: 53	NA	NA	NA	NA	Anterolateral: 43Posterosuperior: 14	Anterolateral: 47Posterosuperior: 10	NA	NA	NA	NA

LH, laparoscopic hepatectomy; OH, open hepatectomy; M/F, male/female; PSM, propensity score matching.
NA, not applicable.

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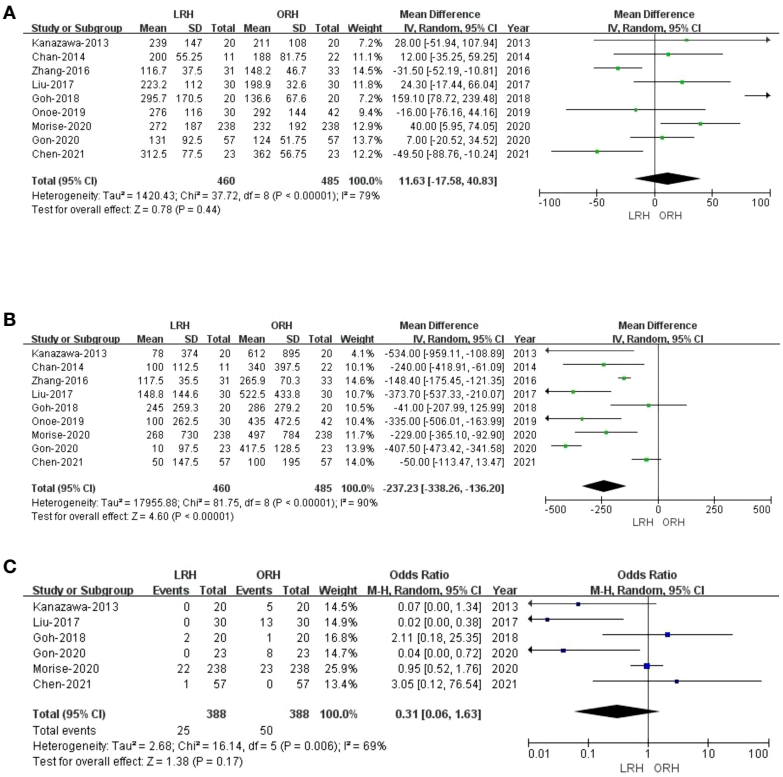

FIGURE 2
Forest plot of comparison of LRH versus ORH for operative outcomes of survivors.**(A)**, Forest plot for operative time; **(B)**, Forest plot for bleeding volume; **(C)**, Forest plot for blood transfusion.

TABLE 2 Summary results of the meta-analyses.

Outcomes of interest	Studies, n	LRH	ORH	MD/OR (95% CI)	P value	Heterogeneity				Evidence quality
						X^2	df	I^2, %	P value	
Operative outcomes										
Operative time	9	460	485	11.63 (-17.58,40.83)	0.44	37.72	8	79	<0.00001	Low
Bleeding volume	9	460	485	-237.23 (-338.26, -136.20)	<0.00001	81.75	8	90	<0.00001	Very low
Blood transfusion	6	388	388	0.31 (0.06, 1.63)	0.17	16.14	5	69	0.006	Low
Postoperative outcomes										
Overall complication rates	8	429	452	0.44 (0.17, 1.14)	0.09	19.29	7	64	0.007	Low
Length of stay	9	460	485	-2.52 (-4.27, -0.76)	0.005	55.68	8	86	<0.00001	Low
90-Day mortality	4	308	308	1.00 (0.25, 4.06)	1.00	1.96	2	0	0.37	Moderate
Oncological outcomes										
1-year overall survival rate	3	279	290	0.60 (0.41,0.89)	0.01	2.50	2	20	0.29	Moderate
3-year overall survival rate	2	268	268	1.06 (0.31,3.62)	0.93	3.30	1	70	0.07	Low
5-year overall survival rate	2	268	268	0.76 (0.44,1.32)	0.33	1.44	1	31	0.23	Moderate
1-year recurrence-free survival rate	5	330	343	1.25 (0.53,2.92)	0.61	12.16	4	67	0.02	Low
3-year recurrence-free survival rate	3	288	288	2.41 (0.62,9.30)	0.20	9.84	2	80	0.07	Low
5-year recurrence-free survival rate	2	268	268	0.85 (0.16,4.46)	0.85	2.98	1	66	0.08	Low

LRH, laparoscopic repeat hepatectomy; ORH, open repeat hepatectomy; MD, mean difference; OR, odds ratio; CI, confidence interval.

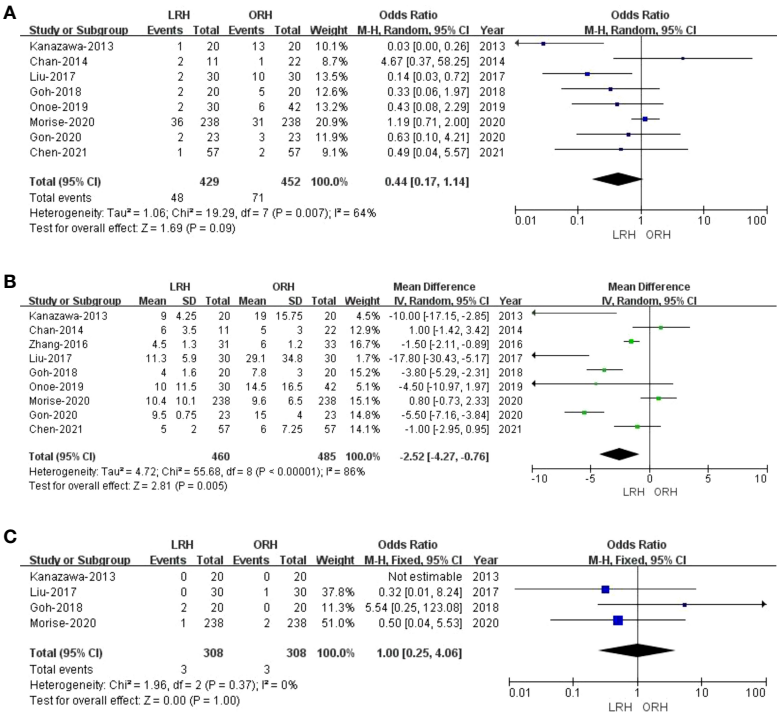

FIGURE 3
Forest plot of comparison of LRH versus ORH for postoperative outcomes of survivors. **(A)**, Forest plot for overall complication rates; **(B)**, Forest plot for the length of stay; **(C)**, Forest plot for 90-day mortality.

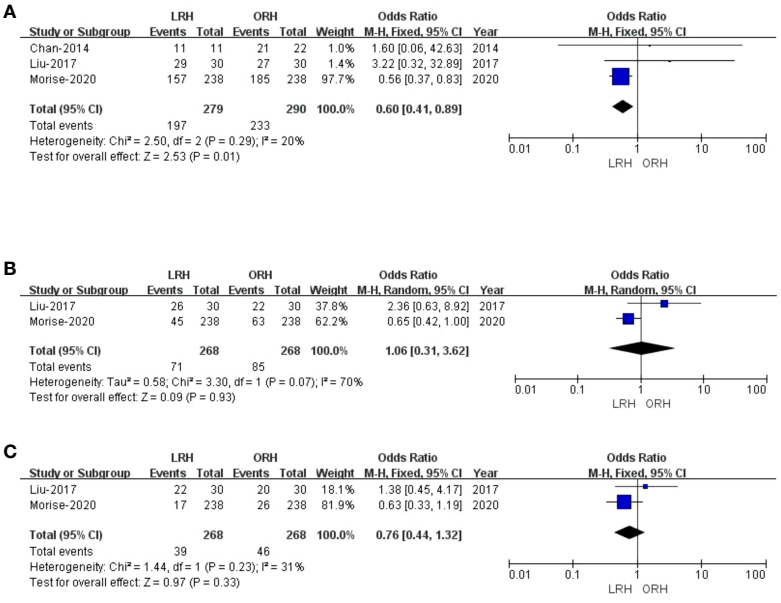

FIGURE 4
Forest plot of comparison of LRH versus ORH for the overall survival rate of survivors. **(A)**, Forest plot for 1-year overall survival time rate; **(B)**, Forest plot for 3-year survival time rate; **(C)**, Forest plot for 5-year survival time rate.

3.5.2 Recurrence-free survival

There were five studies (27–29, 31, 34) that encompassed 673 patients (330 who underwent LRH and 343 who underwent ORH) that evaluated a 1-year recurrence-free survival rate. Overall, the 1-year recurrence-free survival rate did not differ significantly between the two groups (OR: 1.25; 95% CI: 0.53 to 2.92; p = 0.61), with high heterogeneity (I^2 = 67%) in the REM (Figure 5A). Three studies (27–29) reported a 3-year recurrence-free survival rate. The result of the comprehensive analysis revealed no difference in the 3-year recurrence-free survival rate between the two regimens (OR: 2.41; 95% CI: 0.62 to 9.30; p = 0.20), with high heterogeneity (I^2 = 80%) in the REM (Figure 5B). Additionally, two studies (27, 29) traced a 5-year recurrence-free survival rate, and the pooled data indicated no difference in the 5-year recurrence-free survival rate between LRH and ORH groups (OR: 0.85; 95% CI: 0.16 to 4.46; p = 0.85), with low heterogeneity (I^2 = 66%) in the FEM (Figure 5C).

3.6 Publication bias

Begg's funnel plot was used to assess potential publication bias. All studies lie inside the 95% CIs in the funnel plot of 90-day mortality which indicated no potential publication bias (Figure 6).

4 Discussion

For the past few years, the feasibility and efficacy of LRH for RHCC compared to ORH remained ambiguous. In our latest meta-analysis of nine studies and 945 patients with post-hepatectomy HCC recurrence, we confirmed that patients with LRH had a less bleeding volume and shorter hospital stays. However, the one-year survival rate for LRH was lower than that for ORH No significant intergroup differences were observed in other operative or postoperative outcomes, with similar findings in OS and RFS.

Currently, evidence on the role of LRH in the treatment of RHCC is limited (28). Abdominal adhesions have been reported in 67%–93% of patients following abdominal surgery, particularly in patients with severe portal hypertension (30, 35). Such adhesions restricted liver mobilization and made the recognition of vital blood vessels and specific anatomical structures more difficult, which could lead to accidental vascular or biliary damage (30). Handling the serried or vascularized adhesions, especially those around the hepatic hilum or hepatoduodenal ligaments, presented manipulation challenges for LRH (27, 31). In addition to this, deformation in anatomy, formation of collateral circulation, and impaired liver function due to surgical excision of liver parenchyma may attribute to intractability in re-resection (27). Furthermore, laparoscopic resection may lead to inadequate tumor clearance

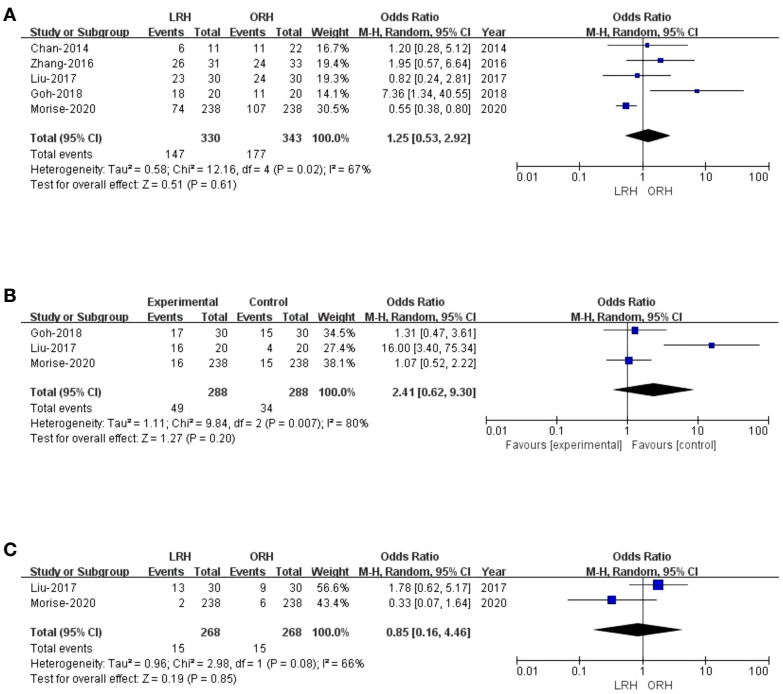

FIGURE 5
Forest plot of comparison of LRH versus ORH for the recurrence-free survival rate of survivors **(A)**, Forest plot for 1-year recurrence-free survival rate; **(b)**, Forest plot for 3-year recurrence-free survival rate; **(C)**, Forest plot for 5-year recurrence-free survival rate.

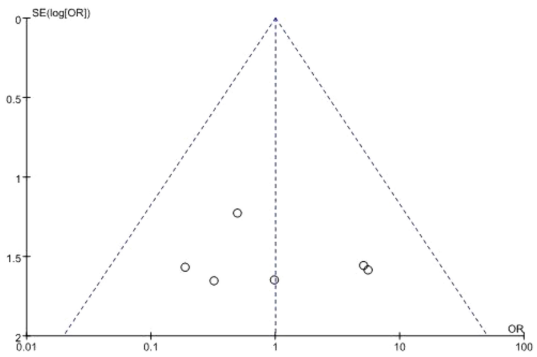

FIGURE 6
Funnel plot for publication bias.

due to the consideration of surgical margin (36). In particular, tumors located in the caudate lobe or seventh or eighth segment have poor visibility, angular transverse lines, and difficulty in operation limited by costal margin and dynamic diaphragms.

However, with the improvement of optical technology, the magnified view provided by laparoscopy had greatly enhanced the visual preciseness in identifying vital structures (31). Moreover, modern laparoscope cameras together with the pneumoperitoneum made the adhesion bands tense up, contributing to a more precise dissection (37). On the other hand, the positive pressure of CO_2 pneumoperitoneum, intraoperative ultrasound, advanced transection devices, facilitation of liver inflow and outflow control, and proficient laparoscopic skills gradually lessened the uncontrollable bleeding under a laparoscope (38). Consequently, previous abdominal operations were not an absolute contraindication for the LRH (35, 39, 40). Specific selection criteria for patients performing LRH had been documented by Hu et al.: tumor located in segments 2–6, a maximum size of 5 cm, no major vessels invaded by tumors, and well-preserved liver function (41).

During the laparoscopic surgery, open techniques were used to insert the first trocar. Pneumoperitoneum was established at 12–14 mmHg, followed by insertion of remaining four to five additional trocars. Ultrasonic surgical aspiration, an ultrasonic system, and a bipolar clamp coagulation system were utilized during the operation. Resection specimens were stored in plastic bags and removed through a small incision at the umbilical site. A midline and subcostal incision was made when performing ORH procedure. A drainage tube was routinely inserted around the cut surface after operation.

Consistent with the previous meta-analyses by Peng et al. and Cai et al., we reported the advantage of LRH in bleeding volume and hospital stay over ORH. Regrettably, they enrolled only seven and six articles, including 433 and 335 patients, respectively. However, we eliminated studies comprising HCC from colorectal cancer metastasis (42–44) and replenished five pieces of literature that were published after December 2018. Furthermore, shorter hospital stay and less intraoperative blood loss were also demonstrated by Chen et al., which included 12 studies published before 1 October 2020. We included an article that was not detected by Chen. et al, as well as their PSM research. Meanwhile, five studies containing metastatic liver cancer were excluded since they violated our definition of RHCC. Through a rigorous screening and analysis process, we reached conclusions similar to those of other meta-analyses. This may be related to fewer injuries, sooner postoperative activity time, and faster bowel function recovery.

This meta-analysis comprehensively updated the security and effectiveness of LRH and ORH. However, several limitations should also be noted. Firstly, the study design of enrolled original studies was diverse, including retrospective survey, prospective study, case-match analysis, and propensity score matching (PSM). Although the PSM method can minimize selection bias and control unit balance, it will never replace randomized controlled trials on account of inherent flaws in research design. For instance, different studies performed PSM based on different potential influencing factors, and the selected factors might be inconsistent or incomplete. Besides, PSM cannot control for unknown confounders or any covariates that were either not measured or erroneously measured. In addition, retrospective studies might result in significant heterogeneity. Thus, further high-quality research is required to confirm the benefit of LRH. Secondly, the substantial heterogeneity in bleeding volume and postoperative hospital stay indicated that the conclusion should be interpreted with caution. Except for study designs, the baseline characteristics of patients, location and quantity of RHCC, surgical equipment, procedure, etc., could attribute to the heterogeneity. Thirdly, in practice, many patients were considered unsuitable for laparoscopic procedures before surgery but were then used as comparisons between laparotomy and laparoscopic interventions. However, we

could not gather data about how many laparoscopic patients were deemed unfeasible. Moreover, included primary studies and our meta-analysis did not evaluate the disease's overall burden.

There was a higher likelihood that patients undergoing LRH might previously have less complicated HCC/liver disease and resection. This selection bias should be highlighted. Finally, all of the primary research was conducted in Asia, with a particular focus on East Asia. Nevertheless, patient characteristics and diagnostic-therapeutic algorithms frequently differ from those endorsed by Western countries. Thus, we need more research from other regions, to verify the applicability of our study.

Conclusion

Collectively, we found that LRH was likely considered a more favorable approach than ORH in specific RHCC cases for the similar risk of oncological outcomes and a quicker recovery from the procedure. However, accurate indications of LRH should be identified, and more studies are needed to reach an evidence-based conclusion.

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.

Author contributions

HW conceived and designed the study. FH, HL, NL, and JL, participated in the literature search and data collection. FH, HL, and NL analyzed the data and wrote the paper. HW reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form.

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.2022.960204/full#supplementary-material

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EDITED BY
Alessandra Bertacco,
Padua University Hospital, Italy

REVIEWED BY
Matteo Donadon,
Università degli Studi del Piemonte Orientale, Italy
Hisanaga Horie,
Jichi Medical University, Japan
Selman Sokmen,
Dokuz Eylül University, Turkey
Barbara Guinn, University of Hull, United Kingdom

*CORRESPONDENCE
Lu Wang
wangluzl@fudan.edu.cn
Weiping Zhu
wpzhush@hotmail.com

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

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A population-based predictive model identifying optimal candidates for primary and metastasis resection in patients with colorectal cancer with liver metastatic

Xin Jin†, Yibin Wu†, Yun Feng, Zhenhai Lin, Ning Zhang, Bingran Yu, Anrong Mao, Ti Zhang, Weiping Zhu* and Lu Wang*

Department of Hepatic Surgery, Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, China

Background: The survival benefit of primary and metastatic resection for patients with colorectal cancer with liver metastasis (CRLM) has been observed, but methods for discriminating which individuals would benefit from surgery have been poorly defined. Herein, a predictive model was developed to stratify patients into sub-population based on their response to surgery.

Methods: We assessed the survival benefits for adults diagnosed with colorectal liver metastasis by comparing patients with curative surgery vs. those without surgery. CRLM patients enrolled in the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015 were identified for model construction. Other data including CRLM patients from our center were obtained for external validation. Calibration plots, the area under the curve (AUC), and decision curve analysis (DCA) were used to evaluate the performance of the nomogram compared with the tumor–node–metastasis (TNM) classification. The Kaplan–Meier analysis was performed to examine whether this model would distinguish patients who could benefit from surgery.

Results: A total of 1,220 eligible patients were identified, and 881 (72.2%) underwent colorectal and liver resection. Cancer-specific survival (CSS) for the surgery group was significantly better than that for the no-surgery group (41 vs. 14 months, $p < 0.001$). Five factors were found associated with CSS and adopted to build the nomograms, i.e., age, T stage, N stage, neoadjuvant chemotherapy, and primary tumor position. The AUC of the CRLM nomogram showed a better performance in identifying patients who could obtain benefits in the surgical treatment, compared with TNM classification (training set, 0.826 [95% CI, 0.786–0.866] vs. 0.649 [95% CI, 0.598–0.701]; internal validation set,

0.820 [95% CI, 0.741–0.899] vs. 0.635 [95% CI, 0.539–0.731]; external validation set, 0.763 [95% CI, 0.691–0.836] vs. 0.626 [95% CI, 0.542–0.710]). The calibration curves revealed excellent agreement between the predicted and actual survival outcomes. The DCA showed that the nomogram exhibited more clinical benefits than the TNM staging system. The beneficial and surgery group survived longer significantly than the non-beneficial and surgery group (HR = 0.21, 95% CI, 0.17–0.27, p < 0.001), but no difference was observed between the non-beneficial and surgery and non-surgery groups (HR = 0.89, 95% CI, 0.71–1.13, p = 0.344).

Conclusions: An accurate and easy-to-use CRLM nomogram has been developed and can be applied to identify optimal candidates for the resection of primary and metastatic lesions among CRLM patients.

KEYWORDS

stage M1a colorectal cancer, liver metastases, resection of primary and metastatic lesions, SEER database, nomogram

Background

Colorectal cancer (CRC) is the third most common cancer worldwide, and 50% of patients develop liver metastasis during the course of the disease (1, 2). Among the potential curative therapies, primary and metastatic resection are the primary option to improve the prognosis of patients (3, 4). However, there remains substantial heterogeneity for some patients with resectable colorectal cancer with liver metastasis (CRLM). At present, the tumor–node–metastasis (TNM) staging classification is mainly considered in the prediction of CRLM prognosis (5). However, some studies demonstrates that CRLM patients with the same TNM classification have a different clinical outcome, and many valuable clinical factors are neglected, which are associated with the prognosis of CRLM patients undergoing primary and metastatic resection (6, 7).

More precise categorization is needed to identify those who may benefit more from surgery. Thus, it is necessary to stratify patients based on their preoperative features to provide more individualized treatments. All kinds of prediction models have been developed and validated to overcome the drawback of the TNM classification system (8). Among these models, the nomogram developed based on several independent prediction factors was widely considered an accurate and easy-to-use tool to visualize the prognosis of patients individually (9–12). It has been reported that the C-index of the nomogram predicting the risk of bone metastasis in colorectal cancer reached 0.929 (13).

Although some studies (14–16) have explored the nomogram to predict the prognosis of CRLM patients, they only predicted the overall survival, and they did not inform patients if they could live longer without the surgery. In this study, a new clinical outcome was established, which included a comparison with the median survival time of non-surgical patients. We assumed that patients receiving surgical treatment who lived longer than the median cancer-specific survival (CSS) time of those who did not undergo surgery could benefit from the operation. Based on this unusual clinical outcome, we aimed to investigate the preoperative prognostic factors, develop and validate an effective predictive model, and then make a reference standard based on the possibility of benefit to identify CRLM patients who would benefit from resection of primary and metastatic lesions.

Method

Patient

For this study, the data we analyzed were extracted from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2018, November 2020 submission), which covers approximately 28% of the US population (17). The SEER*Stat, Version 8.3.9, was applied to examine the data for research between 2004 and 2015.

The inclusion criteria for patients were as follows: 1) patients came from the database of "Incidence—SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000-2018)". 2) The International Classification of Diseases for Oncology (ICD-O-3) was used for the CRLM definition. "Site recode ICD-O-3/WHO 2008" was used to record tumor location information, including ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and

cecum. 3) Liver metastasis. 4) Single primary site. 5) The TNM stage was stated as "M1a". "M1a" was confined as "Metastasis limited to a single distant organ except for peritoneum" (6), and "Year of diagnosis" was set to 2004–2015. 7) According to "Histologic Type ICD-O-3", the following pathological types were included in the following: adenocarcinoma (8140), adenocarcinoma arising in a polyp (8210), adenocarcinoma in tubulovillous adenoma (8263), mucinous/colloid adenocarcinoma (8480), and adenosquamous carcinoma (8560).

The exclusion criteria were as follows: 1) less than 20 years old; 2) diagnosed with no positive histology and not only from a death certificate or autopsy; 3) the information about the surgery to the primary site and metastatic lesion was missing; 4) clinical pathological information (tumor size, carcinoembryonic antigen (CEA), T stage, N stage, histologic type, and neoadjuvant chemotherapy) was missing; and 5) survival information (survival month and final cause of death) was missing.

CRLM patients treated in the Shanghai Cancer Center, Fudan University (FUSCC) from 2016 to 2017 were enrolled as an independent external validation set for this study. The included criteria are as follows: 1) over 18 years old; 2) single primary site; 3) diagnosed with positive histology; 4) the TNM stage was stated as "M1a"; and 4) complete demographic data, clinical parameters, TNM stage information, and full follow-up results.

Data collection

The analyzed data included age (<50, 50 ≤ X < 70, and ≥70), sex (male and female), primary site (rectum, and left and right colon), tumor size (>5 and ≤5 cm), CEA (positive and negative/normal), T stage (T1, T2, T3, and T4), N stage (N0, N1, and N2), differentiation grade (Grade I, Grade II, Grade III, Grade IV, and unknown), histologic type (adenocarcinoma and others), neoadjuvant chemotherapy (yes and no), marital status (married, separated/divorced, single, widowed, and unknown), surgery to the primary site (yes and no), and surgery to the metastatic lesions (yes and no). Overall survival (OS), CSS, and survival month were extracted from the SEER database. OS time was defined as the time from diagnosis to death or to the time of data analysis. Living patients were excluded at the time of the last recording. The CSS duration can be calculated from the date of diagnosis to a documented CRC-related death. According to the published papers (18), we identified "Nonprimary surgical procedure to distant site" as the resection of metastatic lesions.

Statistical analysis

The research group was separated into two groups based on therapy, surgery versus non-surgery. Clinical differences (categorical variables) were represented as a number with percentage and compared by using the chi-square test and Fisher's exact test. The Kaplan–Meier (K-M) method and the log-rank test were analyzed in two groups to confirm the influence of surgery on the survival of patients. To identify independent predictors, univariate and multivariate Cox proportional hazards regression analyses were performed. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). Statistical data were analyzed with SPSS 24.0 (IBM Corp, Armonk, NY, USA). All statistical tests were two-sided, and only $p < 0.05$ could be regarded as statistically significant.

Construction and validation of the nomogram

The eligible people receiving surgery were randomly divided into the training and validation cohorts. Patients who survived longer than the median CSS time of those who received no surgery were defined as benefiting from the surgical treatment. According to the univariate and multivariate Cox analyses, the factors independently affecting the CSS were indicated in the training cohort. Based on the multivariable logistic analysis, the nomogram to identify the patients who may obtain benefits from primary and metastasis resection was developed. The areas under the receiver operating characteristic (ROC) curve (AUCs) were applied to quantify ROC performance to assess the discriminative and calibration capacity of the nomograms. Calibration curves were utilized to demonstrate no deviations from the reference line, indicating a high degree of dependability. What is more, the decision curve analysis (DCA) was also used to evaluate the clinical application value and clinical practicability of the models. Overall, we used ROC, calibration plots, and DCA to graphically describe the performance of our model. What is more, we attempted to assign all CRLM patients undergoing surgery to two groups—beneficial and surgery group and non-beneficial and surgery group—in terms of probability of benefit of 50%. The Kaplan–Meier analyses and the log-rank test were employed to test whether this model could identify individuals who could indeed benefit from the resection of primary and metastatic lesions.

Results

Patient characteristics

From the SEER database, 1,220 patients with M1a CRLM who met inclusion criteria were identified from 2004 to 2015. The flowchart is illustrated in Figure 1. Among them, 881 (72.2%) received primary and metastatic resection, while 339 (27.8%) had no surgical treatment. Men predominantly made up 53.4% of these cases, 20.7% of these patients were under the age of 50, and 15.1% of the tumors were in the rectum; 66.2% of tumors were classified as grade II in terms of the differentiation grade. In addition, 80.6% of

patients were CEA-positive. Adenocarcinoma was found in 87.0% of the patients. Also, neoadjuvant chemotherapy was administered to 81.3% of patients. According to the TNM stage classification, 54.3% of the tumor were categorized as T3, and 27.8% of them were categorized as N2. The detailed clinical information of all patients is summarized in Table S1.

Least absolute shrinkage and selection operator regression

In total, 12 variables were incorporated in the least absolute shrinkage and selection operator (LASSO) regression, and all of them were included: age, sex, race, differentiation grade, histology type, T stage, N stage, tumor size, marital status, neoadjuvant chemotherapy, CEA, and primary tumor position (Figure 2).

Kaplan–Meier curves of cancer-specific survival

According to the K-M analysis and log-rank test in the SEER cohort (Figure S1), patients who received excision of primary and metastatic tumors enjoyed a longer CSS. The median CSS time was 41 months (95% CI, 37.15–44.85) for individuals who underwent resection of primary and metastatic tumors, compared to 14 months (95% CI, 11.37–16.63) for patients with no surgery.

Univariable and multivariable analyses

Compared with logistic regression, the Cox analysis focused more on the influence of variables on the survival of CRLM patients. In the univariate and multivariate Cox analyses, age, race, differentiation grade, primary site, T stage, N stage, neoadjuvant chemotherapy, marital status, and CEA were found to be independent predictors for the survival of patients with stage M1a CRLM. However, sex, tumor size, and histology were shown to have no significant impact on CSS (Table 1). Moreover, surgery was found to be independently linked with higher CSS (HR = 0.28, 95% CI, 0.24–0.33, $p < 0.001$), which further indicated the significance of surgery in the treatment.

Definition of benefiting in the surgery

The median CSS time (14 months) of non-surgical patients was considered as the reference line. Patients who underwent curative surgery yielded better CSS than this reference line and were identified to be beneficial in the operation. Conversely, surgical patients whose CSS was lower than 14 months were considered non-beneficial patients. A total of 708 (80.36%) patients were categorized as "beneficial". The characteristics of patients are presented in Table 2.

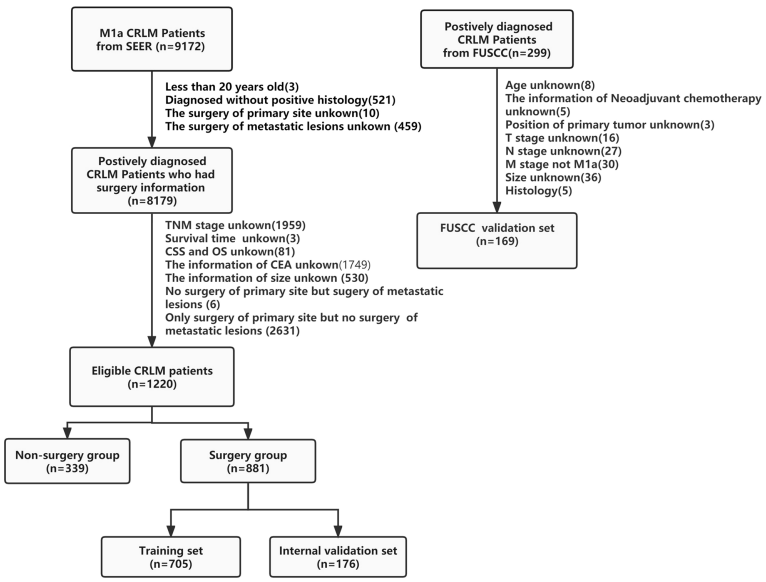

FIGURE 1
Flowchart of the data selection process.

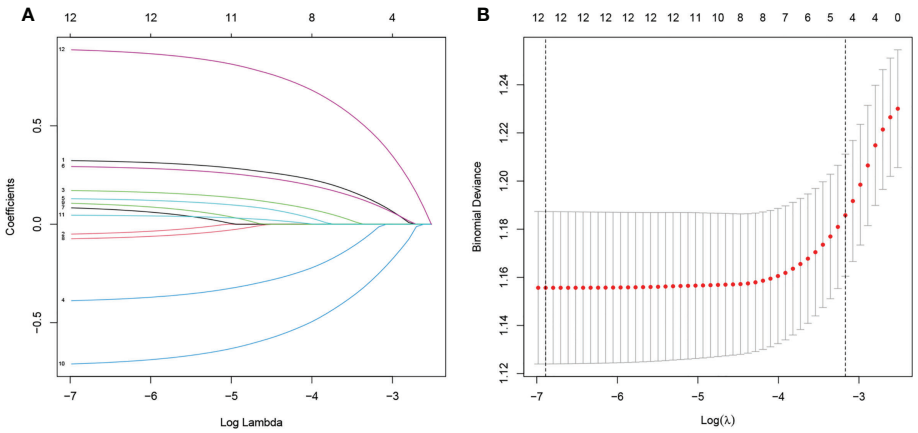

FIGURE 2
(A) Plot of partial likelihood deviance of CSS. **(B)** LASSO coefficient profile plot of CSS. CSS, cancer-specific survival; LASSO, least absolute shrinkage and selection operator.

Construction and internal validation of the nomogram

We randomly assigned 881 patients who underwent curative surgery in a 4:1 ratio to the training cohort (n = 705) and the validation cohort (n = 176). The median CSS time of the training cohort and validation cohort was 41 [36.74–45.26] and 40 [31.34–48.66] months, respectively.

Nine independent predictors including age, race, differentiation grade, T stage, N stage, neoadjuvant chemotherapy, marital status, CEA, and primary tumor position were collected into the multivariate logistic regression. We identified five effective factors and developed a nomogram to predict the stage M1a CRLM patients who could benefit from the surgical treatment based on the training cohort (Figure 3; Table 3).

ROC analysis demonstrated the AUCs of the training and validation cohorts reached 0.826 [95% CI, 0.786–0.866] and 0.820 [95% CI, 0.741–0.899], respectively, outperforming the American Joint Committee on Cancer (AJCC)–TNM classification of 0.649 [95% CI, 0.598–0.701] and 0.635 [95% CI, 0.539–0.731], respectively (Figures 4A, B). In addition, the performance of the model was visualized by the calibration plots, and the calibration curves showed good agreement between prediction and observation (Figures 4C, D). Finally, DCA showed a higher clinical application value and better clinical practicability (Figure 5).

External validation

In this study, external validation was performed in the FUSCC cohort. The AUC of the CRLM nomogram was 0.763 [95% CI, 0.691–0.836], outperforming the AJCC-TNM classification of 0.626 [95% CI, 0.542–0.710] (Figure S5A). Moreover, both DCA and the calibration curves of the CRLM nomogram demonstrated better performance compared with the TNM classification (Figures S5B, C).

Development of webserver for easy access to nomogram

According to the above results, a dynamic web-based probability calculator (Dynamic Nomogram (shinyapps.io)) was constructed at https://fuscliver.shinyapps.io/dynnomapp/ to identify optimal candidates for surgery based on the previous nomogram. The predicted probability of benefit in the surgery can be simply calculated by inputting clinical characteristics and viewing the output of the webserver's output figures and tables.

Risk stratification system

According to the Kaplan–Meier analysis and log-rank test, the beneficial and surgery group had a considerably longer survival time than the non-beneficial and surgery group (HR = 0.21, 95% CI, 0.17–0.27, p < 0.001). However, no significant difference was found between the non-beneficial and surgery and non-surgery groups (Figure 6) (HR = 0.89, 95% CI, 0.71–1.13, p = 0.344).

Discussion

In the present study, a nomogram including age, T stage, N stage, neoadjuvant chemotherapy, and primary tumor

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TABLE 1 Univariable and multivariate Cox analyses for CSS among CRLM patients.

	Univariable		Multivariable	
	Adjust HR (95% CI)	p-Value	Adjust HR (95% CI)	p-Value
Age				
<50	References		References	
50 ≤ X < 70	1.34 (1.12–1.62)	0.001	1.14 (0.95–1.38)	0.16
≥70	2.67 (2.17–3.27)	<0.001	1.53 (1.21–1.93)	<0.001
Sex				
Female	References			
Male	0.93 (0.81–1.06)	0.274		
Size				
≤3 cm	References		References	
3 < X ≤ 5 cm	0.88 (0.72–1.07)	0.204	0.84 (0.69–1.03)	0.1
5 < X ≤7 cm	1.07 (0.87–1.32)	0.534	0.95 (0.76–1.18)	0.63
>7 cm	1.45 (1.16–1.83)	0.001	1.19 (0.93–1.51)	0.17
Race				
Black	References		References	
White	0.82 (0.69–0.98)	0.029	0.84 (0.70–1.01)	0.062
Other	0.61 (0.46–0.82)	<0.001	0.60 (0.45–0.81)	0.001
Grade				
I	References		References	
II	0.87 (0.59–1.29)	0.48486	0.96 (0.65–1.44)	0.852
III	1.51 (1.00–2.29)	0.05247	1.57 (1.03–2.40)	0.04
IV	1.48 (0.88–2.46)	0.13615	1.86 (1.10–3.14)	0.02
Unknown	1.93 (1.27–2.95)	0.002	1.17 (0.75–1.81)	0.5
Histology				
Other	References			
Adenocarcinoma	1.16 (0.95–1.42)	0.155		
T stage				
T1	References		References	
T2	0.21 (0.13–0.34)	<0.001	0.43 (0.26–0.71)	0.001
T3	0.36 (0.30–0.43)	<0.001	0.75 (0.60–0.95)	0.019
T4	0.57 (0.47–0.70)	<0.001	1.03 (0.81–1.32)	0.785
N stage				
N0	References		References	
N1	0.74 (0.63–0.86)	<0.001	1.08 (0.91–1.29)	0.377
N2	0.82 (0.69–0.97)	0.021	1.45 (1.18–1.80)	<0.001
Neoadjuvant chemotherapy				
No	References		References	
Yes	0.27 (0.23–0.31)	<0.001	0.29 (0.24–0.34)	<0.001
Marital status				
Married	References		References	
Separated or divorced	1.23 (0.99–1.52)	0.067	0.92 (0.74–1.15)	0.478
Single	1.28 (1.07–1.52)	0.006	1.21 (1.01–1.45)	0.04
Widowed	2.10 (1.68–2.61)	<0.001	1.22 (0.96–1.55)	0.1
Unknown	1.28 (0.87–1.88)	0.206	1.10 (0.74–1.63)	0.633
CEA				
Negative/normal	References		References	
Positive/elevated	1.89 (1.56–2.28)	<0.001	1.86 (1.53–2.26)	<0.001
Primary tumor position				

(Continued)

TABLE 1 Continued

	Univariable		Multivariable	
	Adjust HR (95% CI)	p-Value	Adjust HR (95% CI)	p-Value
Left colon	References		References	
Right colon	1.63 (1.41–1.89)	<0.001	1.49 (1.28–1.74)	<0.001
Rectum	1.07 (0.87–1.32)	0.517	0.92 (0.74–1.14)	0.438
Surgery				
No	References		References	
Yes	0.28 (0.24–0.33)	<0.001	0.30 (0.25–0.38)	<0.001

CRLM, colorectal cancer with liver metastasis; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.
$p < 0.05$ means the result is statistically significant.

position was constructed and validated to identify optimal candidates for the primary and metastatic resection. In clinical practice, our nomogram can aid clinicians in the process of making decisions as a convenient and accurate predictive model.

Five factors were considered into account in our model in this study and were attached to different risk scores, which could indicate the impact they did on the decision. Present results supported our hypothesis and revealed some significant discoveries. Our nomogram shared several parameters with previous studies on CRLM survival prediction. Some factors marked with a high-risk score in our model, like T stage, age, neoadjuvant chemotherapy, and primary tumor position, were also generally recognized in other studies (12, 15, 16, 19, 20).

For the first time, age was indicated to correlate with the potential of benefit strongly. A growing body of evidence suggests that the elderly have a poorer prognosis, which is consistent with our result (21–23). The elderlies undergoing surgery usually have poor physical and mental health, which has a bad effect on the subsequent adjuvant therapy. What is more, due to neglect of regular physical examination, the tumor is often at an advanced stage when discovered.

In our nomogram, the T1 stage had the least risk scores, indicating that patients with T1-stage tumors are unlikely to benefit from surgery. This distinct phenomenon went against common sense. However, the research of Lupo Wu also noticed this phenomenon and attributed it to the distinct genetic profile of the T1 stage tumors (24). This finding indicated that more attention should be paid to the surveillance and the screening of CRLM with early T stage.

The primary tumor sites served as a high-ranking risk factor, which could affect the potential surgery benefit in our models, and other studies have also confirmed this observation (20, 25, 26). Patients with left-sided tumors often had a better survival outcome than those with right-sided tumors, with a longer CSS of 89 vs. 78 months ($p = 0.001$) in a SEER cohort (27). Moreover, a national multi-center retrospective study launched by Shida demonstrated that right-sided CRC (RCRC) patients had worse OS than left-sided CRC (LCRC) patients (22). Some studies revealed that histological and molecular characteristics played an important role in this phenomenon (22, 28–30). The gene profile of RCRC and LCRC is completely different. RCRC was mostly diploid with high microsatellite instability, mucinous histology, CpG island methylation, and BRAF mutation, which made RCRC tend to have a more advanced clinical behavior than LCRC. Conversely, LCRC has frequent p53 and KRAS mutations (29, 31). Additionally, it is more difficult to detect RCRC at an early stage because of its flat morphology in the screening of colonoscopy (32, 33). Therefore, the primary lesion of RCRC is often discovered in more advanced stages than that of LCRC.

The tumor size and grade demonstrated a correlation to CSS based on LASSO regression. Nevertheless, the strength of correlation cannot meet the criteria for multiple variable Cox and logistic regression. Therefore, they were excluded from our prediction models. A similar outcome was found in other CRLM studies (12, 15, 16). Conversely, sex was proved that it had a certain effect on the outcome in Kattan's research (19), and we attributed the cause to the difference between the data from different centers for this conflict.

Additionally, our research demonstrated that carcinoembryonic antigen (CEA) was associated with OS and CSS in LASSO regression. Some studies have indicated that preoperative serum CEA level plays a significant role in the prognosis of CRC patients as an independent risk factor for prognosis (34–37). However, CEA was not statistically meaningful for CSS while performing multi-logistic regression in our study. Hence, we made a new nomogram including CEA (Figure S2), of which AUC [training 0.829 95% CI, 0.790–0.869, validation 0.843 95% CI 0.772–0.913] and calibration plots (Figures S3C, D) show no significant difference between the new nomogram and the former. That is to say, the prediction

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TABLE 2 Characteristics of M1a CRLM patients who benefit from the surgery.

Parameters	All surgery M1a CRLM patientsn = 881 (%)	Non-beneficial n = 173 (%)	Beneficial n = 708 (%)	p-Value
Age				<0.001
<50	214 (24.3)	17 (9.8)	197 (27.8)	
50 ≤ X < 70	483 (54.8)	77 (44.5)	406 (57.4)	
≥70	184 (20.9)	79 (45.7)	105 (14.8)	
Sex				0.099
Female	414 (47.0)	91 (52.6)	323 (45.6)	
Male	467 (53.0)	82 (47.4)	385 (54.4)	
Size				0.007
≤3 cm	146 (16.6)	22 (12.7)	124 (17.5)	
3 < X ≤ 5 cm	376 (42.7)	68 (39.3)	308 (43.5)	
5 < X ≤ 7 cm	227 (25.7)	43 (24.9)	184 (26.0)	
>7 cm	132 (15.0)	40 (23.1)	92 (13.0)	
Race				0.544
Black	135 (15.3)	21 (12.2)	114 (16.1)	
White	654 (74.2)	135 (78.0)	519 (73.3)	
Other	91 (10.4)	17 (9.8)	74 (10.5)	
Unknown	1 (0.1)	0 (0.0)	1 (0.1)	
Grade				<0.001
I	26 (3.0)	4 (2.3)	22 (3.1)	
II	646 (73.3)	102 (59.0)	544 (76.8)	
III	140 (15.9)	51 (29.5)	89 (12.6)	
IV	38 (4.3)	13 (7.5)	25 (3.5)	
Unknown	31 (3.5)	3 (1.7)	28 (4.0)	
Histology				0.05
Adenocarcinoma	753 (85.5)	156 (90.2)	597 (84.3)	
Other	128 (14.5)	17 (9.8)	111 (15.7)	
T stage				<0.001
T1	20 (2.3)	3 (1.7)	17 (2.4)	
T2	34 (3.8)	2 (1.2)	32 (4.5)	
T3	582 (66.1)	97 (56.1)	485 (68.5)	
T4	245 (27.8)	71 (41.0)	174 (24.6)	
N stage				<0.001
N0	167 (19.0)	17 (9.8)	150 (21.2)	
N1	390 (44.3)	68 (39.3)	322 (45.5)	
N2	324 (36.8)	88 (50.9)	236 (33.3)	
Neoadjuvant chemotherapy				<0.001
No	126 (14.3)	75 (43.4)	51 (7.2)	
Yes	755 (85.7)	98 (56.6)	657 (92.8)	
Marital status				<0.001
Married	528 (59.9)	95 (54.9)	433 (61.2)	
Separated or divorced	85 (9.6)	17 (9.8)	68 (9.6)	
Single	169 (19.2)	25 (14.5)	144 (20.3)	
Widowed	72 (8.2)	30 (17.3)	42 (5.9)	
Unknown	27 (3.1)	6 (3.5)	21 (3.0)	
CEA				0.109
Negative/normal	209 (23.7)	33 (19.1)	176 (24.9)	
Positive/elevated	672 (76.3)	140 (80.9)	532 (75.1)	
Primary tumor position				<0.001

(Continued)

TABLE 2 Continued

Parameters	All surgery M1a CRLM patientsn = 881 (%)	Non-beneficial n = 173 (%)	Beneficial n = 708 (%)	p-Value
Left colon	385 (43.7)	49 (28.3)	336 (47.5)	
Right colon	380 (43.1)	108 (62.4)	272 (38.4)	
Rectum	116 (13.2)	16 (9.3)	100 (14.1)	

CRLM, colorectal cancer with liver metastasis; CEA, carcinoembryonic antigen.
$p < 0.05$ means the result is statically significant.

efficiency can not be greatly improved by taking CEA into account. The ROC of the new nomogram is shown in Figures S3A, B.

During the study, we were puzzled by the differences between surgical and non-surgical patients (Table S1), which are mainly in the field of grade, T stage, and N stage. It was difficult to understand the fact that many patients with grade II, T1, or N0 staging were treated with no surgery, which is contrary to our previous perception. We believe that the reason for these incredible differences is the changes in the treatment modality for CRLM patients. With the development of medical technology, more and more CRLM patients were identified to be able to obtain survival benefits in surgical treatment, and surgery becomes the first choice for patients' treatment. In our study, some people who lived in the time when the benefit of surgical treatment was not recognized were included. Although their condition was considered to meet the criteria for surgery now, they were not suggested to receive the surgery.

Compared with the nomogram currently published about predicting the prognosis of CRLM patients (5), our model performs better in terms of the accuracy of the nomogram.

What is more, CRLM patients diagnosed between 2004 and 2015 from the SEER database were collected for model construction and internal validation. An independent dataset was obtained from China for external validation. As a well-known database, the SEER database has larger and multi-center data compared with the limited data of our own center, which can improve the model's predictive performance. However, these are two datasets covering highly different epidemiological, genetic, molecular, and cultural backgrounds, which are not free from potential selection bias.

However, there are still several limitations in the present study. Firstly, some factors reported to be significant for the prognosis of CRLM patients such as the number and size of liver metastasis were not investigated in this study because of the lack of relevant information (12, 15). Despite the lack of that information, our model still demonstrates a better performance for identifying CRLM patients than the TNM stage system, which encouraged us to continue this study. In the future, we are going to collect multi-center data to develop a modified CRLM (m-CRLM) nomogram that takes other significant indicators such as the size and number of liver metastases into account, in order to make our predicting tool

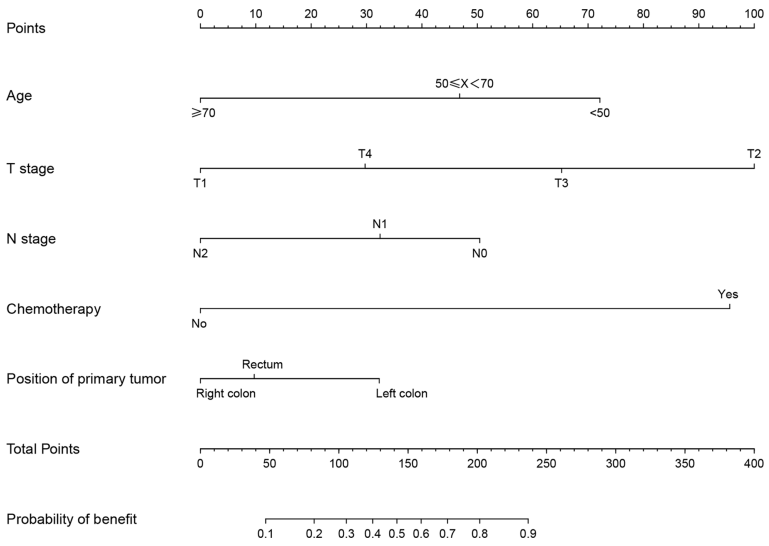

FIGURE 3
Construction of the CRLM nomogram. CRLM, colorectal cancer with liver metastasis.

TABLE 3 Multivariate logistic analysis among M1a CRLM patients.

	Multivariate	
	OR (95% CI)	**p-Value**
Age		
<50	Reference	
50 ≤ X < 70	0.57 (0.29–1.13)	0.109
≥70	0.21 (0.10–0.45)	<0.001
Race		
Black	Reference	
White	0.63 (0.30–1.31)	0.217
Other	0.60 (0.22–1.60)	0.305
Grade		
I	Reference	
II	1.02 (0.29–3.60)	0.971
III	0.46 (0.12–1.75)	0.255
IV	0.54 (0.12–2.45)	0.423
Unknown	1.64 (0.26–10.27)	0.598
T stage		
T1	Reference	
T2	9.99 (1.23–80.97)	0.031
T3	5.14 (1.20–22.07)	0.028
T4	2.46 (0.56–10.78)	0.234
N stage		
N0	Reference	
N1	0.76 (0.37–1.53)	0.439
N2	0.37 (0.18–0.76)	0.007
Neoadjuvant chemotherapy		
No	Reference	
Yes	9.30 (5.22–16.59)	<0.001
Marital status		
Married	Reference	
Separated or divorced	0.93 (0.43–2.02)	0.852
Single	1.07 (0.56–2.04)	0.836
Widowed	0.77 (0.36–1.63)	0.491
Unknown	0.81 (0.21–3.07)	0.756
CEA		
Negative/normal	Reference	
Positive/elevated	0.57 (0.32–1.02)	0.059
Primary tumor position		
Left colon	Reference	
Right colon	0.52 (0.31–0.87)	0.013
Rectum	0.63 (0.30–1.34)	0.23

CRLM, colorectal cancer with liver metastasis; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.
$p < 0.05$ means the result is statistically significant.

more comprehensive and reliable. Secondly, the median CSS time is unable to reflect the overall survival characteristic of the non-surgical group, and some reference standards that could represent the prognostic status of the unoperated patient comprehensively are worthy of further research. Thirdly, due to the relatively limited amount of validation set, the performance of this model is still needed to be confirmed in a larger and prospective cohort.

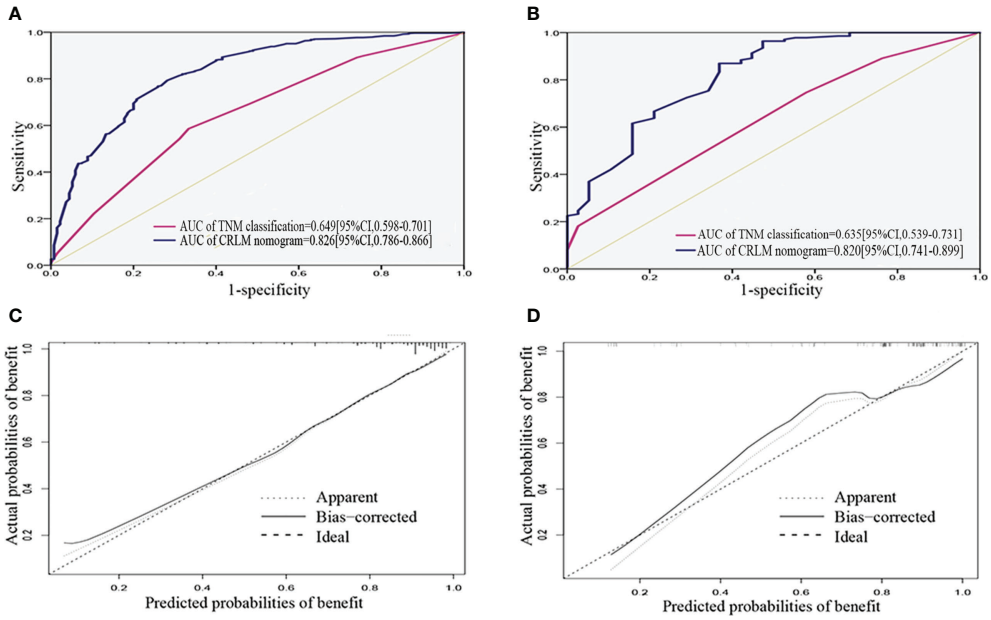

FIGURE 4
Validation of the nomogram. **(A, B)** ROC curve for discrimination in the training and validation cohorts. **(C, D)** Calibration plots for the actual (observed) and predicted probabilities of the nomograms in the training and validation cohorts. ROC, receiver operating characteristic curve.

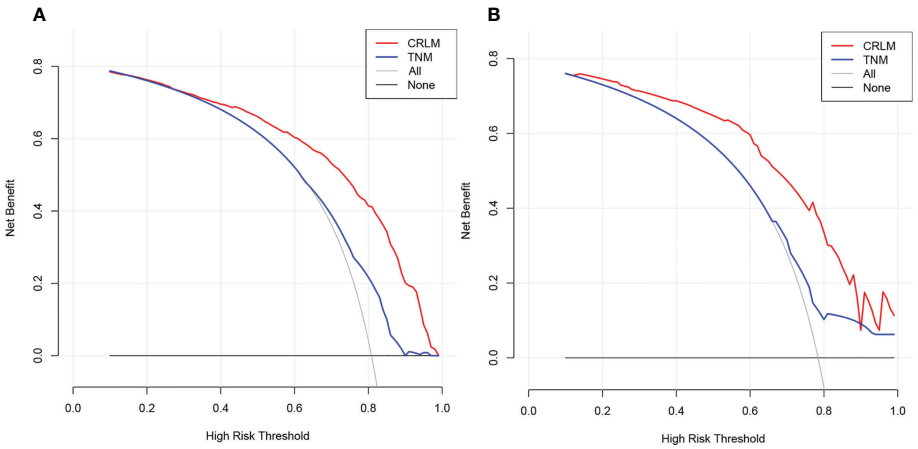

FIGURE 5
Decision curve analysis of CRLM nomogram in the training **(A)** and validation **(B)** cohorts. Horizontal lines indicate that no cases will experience the event. Gray lines indicate that all cases will experience the event. Red and blue lines represent the net benefits across threshold probabilities according to the CRLM nomogram and TNM classification, respectively. CRLM, colorectal cancer with liver metastasis..

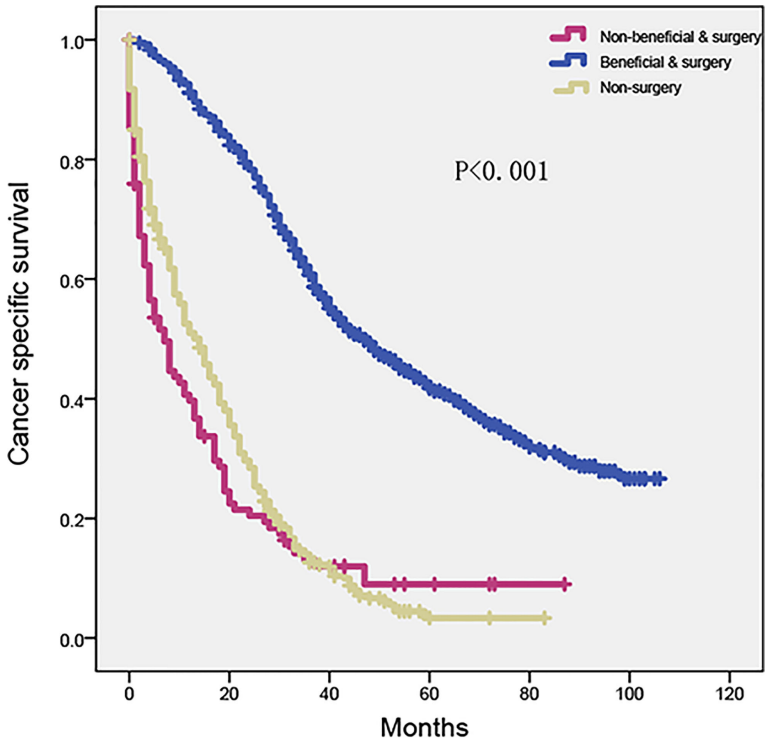

FIGURE 6
Kaplan–Meier plot to differentiate beneficial group according to CRLM nomogram in SEER cohort. SEER, Surveillance, Epidemiology, and End Results; CRLM, colorectal cancer with liver metastasis.

Conclusion

In summary, we have provided a novel and simple model to identify stage M1a CRLM patients who could indeed benefit from surgery. This predicting model could output individualized results with good accuracy, availability, and applicability. This nomogram might influence the clinician's decision making in the process of treatment.

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

XJ and YW designed the study. XJ, YW, YF, and ZL collected the data and analyzed the data. XJ and YW drafted the manuscript. TZ, BY, and NZ reviewed the manuscript. WZ and LW were responsible for the whole project and supervised the study. 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.2022.899659/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan-Meier plot of CSS in stage M1a CRLM patients according to primary and metastatic resection. CSS, cancer specific survival; CRLM, colorectal cancer with liver metastasis.

SUPPLEMENTARY FIGURE 2
Construction of the new CRLM nomogram with the addition of CEA. CRLM, colorectal cancer with liver metastasis; CEA, carcinoembryonic antigen.

SUPPLEMENTARY FIGURE 3
Validation of the new CRLM nomogram. (A, B) ROC curve for discrimination in the training and validation cohorts. (C, D) Calibration plots for the actual (observed) and predicted probabilities of the new CRLM nomograms in the training and validation cohorts.

SUPPLEMENTARY FIGURE 4
Decision curve analysis of new CRLM nomogram with the addition of CEA in the training and validation cohorts. Horizontal lines indicates that no cases will experience the event; Gray lines indicates that all cases will experience the event; Red and blue lines represent the net benefits across threshold probabilities according to the CRLM nomogram and TNM classification, respectively. CRLM, colorectal cancer with liver metastasis; TNM, tumor, node, and metastasis; CEA, carcinoembryonic antigen.

SUPPLEMENTARY FIGURE 5
External validation of the nomogram. (A) ROC curve for discrimination in the FUSCC cohorts. (B) Calibration plots for the actual (observed) and predicted probabilities of the nomogram in the FUSCC cohorts. (C) Decision curve analysis of CRLM nomogram in the FUSCC cohorts. ROC, receiver operating characteristic curve; FUSCC, Shanghai Cancer Center, Fudan University.

SUPPLEMENTARY TABLE 1
Characteristics of M1a CRLM patients.

SUPPLEMENTARY TABLE 2
Characteristics of training set, internal and external validation set.

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EDITED BY
Jens Uwe Marquardt,
University of Lübeck, Germany

REVIEWED BY
Jens Hoeppner,
University Medical Center Schleswig-Holstein, Germany
Vincenzo Lizzi,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy

*CORRESPONDENCE
Luca Morelli
luca.morelli@med.unipi.it

†These authors have contributed equally to this work

‡These authors have contributed equally to this work and share senior authorship

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Surgery combined with intra-operative microwaves ablation for the management of colorectal cancer liver metastasis: A case-matched analysis and evaluation of recurrences

Simone Guadagni[1†], Federica Marmorino[2,3†], Niccolò Furbetta[1], Martina Carullo[2,3], Desirée Gianardi[1], Matteo Palmeri[1], Gregorio Di Franco[1], Annalisa Comandatore[1], Roberto Moretto[2], Elisa Cecilia[1], Giovanni Dima[2,3], Gianluca Masi[2,3], Chiara Cremolini[2,3], Giulio Di Candio[1‡] and Luca Morelli[1‡*]

[1]General Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [2]Unit of Oncology 2, University Hospital of Pisa, Pisa, Italy, [3]Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy

Background: Hepatic resection is the only chance of cure for a subgroup of patients with colorectal cancer liver metastasis. As the oncologic outcomes of intra-operative microwaves ablation combined with hepatic resection still remain uncertain in this setting, we aimed to compare this approach with surgery alone in patient's candidate to metastases resection with radical intent.

Methods: Using a case-matched methodology based on age, gender, American Society of Anesthesiology score, Body Mass Index, and burden that take in consideration the number and maximum size of lesions, 20 patients undergoing hepatic resection plus intra-operative microwaves (SURG + IMW group) and 20 patients undergoing hepatic resection alone (SURG group), were included. Relapse-free Survival and post-resection Overall Survival were compared between patients of two groups.

Results: At the median follow up of 22.4 ± 17.8, 12/20 patients (60%) in SURG +IMW group and 13/20 patients (65%) in the SURG group experienced liver metastasis recurrence (p=0.774). None of them had recurrence at the same surgical or ablation site of the first hepatic treatment. 7/12 patients in the SURG+IMW group and 7/13 patients in the SURG group underwent at least one further surgical treatment after relapse (p = 1.000). No difference was reported between the two groups in terms of Relapse-free Survival (p = 0.685) and post-resection Overall Survival (p = 0.151). The use of intra-operative microwaves

was not an independent factor affecting Relapse-free Survival and post-resection Overall Survival at univariate and multivariate analysis.

Conclusions: Patients with colorectal cancer liver metastasis undergoing surgery plus intra-operative microwaves have similar post-operative results compared with surgery alone group. The choice between the two approaches could be only technical, depending on the site, number, and volume of the metastases. This approach could also be used in patients with liver metastasis relapse who have already undergone hepatic surgery.

KEYWORDS

liver metastasis, colorectal cancer, microwaves, liver resection, Thermal Ablation

Introduction

Over the last decades, the outcomes of patients with colorectal cancer liver metastases (CRCLM) have greatly improved thanks to innovations in surgical and ablation techniques, more effective systemic therapeutic regimens and the crucial role of a multidisciplinary management, all factors that have allowed to widely extend the indication for surgery with curative intent, even in patients initially defined unresectable (1, 2).

Parenchymal sparing surgery (PSS) has progressively replaced major hepatectomies, becoming the standard of care for patients with CRCLM suitable for surgery, as it has demonstrated advantages in terms of postoperative complications and of liver function preservation, while ensuring similar oncological outcomes (3). Possible drawbacks of this approach may be related to deep-located lesions, which management can be difficult, potentially causing increased blood loss, a sacrifice of a disproportionate amount of parenchyma compared to the size of the lesion, and inevitably prolonging operative time. In this setting, intra-operative thermal-ablation may represent an appealing alternative that can be combined with surgical resection of peripherally located metastases in order to increase the options of treatment for patients with multiple or even bilobar CRCLM.

Nevertheless, the role of surgery combined with intra-operative thermal ablation with curative intent for the treatment of patients affected by CRCLM is still uncertain.

Some studies have reported inferior results of thermal ablation using radiofrequency respect to surgery alone (4–6); however, the possible impact of intra-operative microwaves (IMW) in this specific setting, could be higher than what is currently considered by surgeons.

The present study aims to compare peri-operative and mid-term oncologic outcomes of patients with CRCLM undergoing surgery plus IMW ablation with those of patients undergoing surgery alone, with also a view on the reiterated treatment of hepatic recurrences.

Materials and methods

Patients' selection

We retrospectively analyzed data of all patients with CRCLM undergoing open hepatic resection alone or hepatic resection plus IMW ablation for CRCLM with curative intent at our tertiary care center. Inclusion criteria were the following: i) histologically confirmed diagnosis of CRCLM, ii) patients undergoing hepatic resection or hepatic resection plus IMW with curative intent. Minimally invasive surgery or radio-frequency ablation represented instead exclusion criteria, as well as absence of follow-up and detailed peri-operative information. Patients were then selected by a one-to-one case-matched methodology, where each patient who had undergone surgery plus IMW ablation (SURG+IMW group) was matched with a comparable patient treated with surgical resection alone (SURG group). Matching criteria were the following: age, gender, ASA (American Society of Anesthesiologists) score, BMI (Body Mass Index) and hepatic lesions burden. The hepatic burden was divided into three groups according to the number and maximum size of CRLM: 1-3 lesion and/or maximum size of the biggest lesion of 3 cm (Low burden), 4-10 lesions and/or maximum size of the biggest lesion between 3 and 5 cm (Intermediate burden), more than 10 lesions and/or maximum size of the biggest lesion more than 5 cm (High burden). The study was approved by the Institutional Review Board.

Surgical procedures

In patients with CRCLM treated with PSS, the decision to use IMW instead of surgically resecting every single lesion mainly depended on its dimension and location. In particular, small (up to 40mm), deep located lesions (especially of the right lobe), or those highly complex to be removed for their location and/or vascular relationship (for instance those located at the hepato-caval confluence), were preferentially treated with IMW ablation. On the contrary, superficial lesions easy to be removed without excessive sacrifice of liver parenchyma were surgically removed. Monolobar deeply located larger lesions (>40mm) and monolobar multiple CRLM were instead indications for major hepatectomies. PSS was the preferred approach every time it was possible. In all patients an intraoperative Ultrasound (US) scan was performed by the operating surgeon. A maximum number of lesions or maximum size *a priori* was not established, but the operation was considered with curative intent based on a case-by-case surgeon's judgement of feasibility of radical treatment with surgery alone or surgery + IMW, following the described criteria.

For IMW ablation we used microwaves energy device with AMICA™ generator (Hospital Service, Rome, Italy) and 14 G, 150 mm applicators. The tip of the applicator was directed throughout the hepatic parenchyma under real-time US-guide. We generally used a 40-60 Watt with a total of 2 to 5 minutes in a single energy delivery in order to reach a safe coagulative area.

Surgical removal of metastases was performed either with segmentectomy, wedge resection or metastasectomy with the aid of LigaSure™ "Dolphin Tip" (Medtronic, Milan, Italy). Pringle maneuver was not routinely performed, but in relation to lesions size and location. Anatomical major hepatectomies were taken into consideration in selected cases and were performed with the Lortat-Jacob approach.

Pre-surgical chemotherapy was administered according to disease-related characteristics (clinical presentation, tumour burden, resectability tumour sidedness, and tumour biology) and patient-related factors (performance status, age and comorbidity). All patients were considered for surgery in accordance to oncologists at the multidisciplinary discussion based on surgical and oncological criteria. Among patients treated with pre-operative chemotherapy, no one experienced progression disease after pre-surgery therapy as they were not considered optimal candidate for surgical treatment. Reiterated treatment for recurrences was always considered in accordance to oncologists after multidisciplinary discussion, with both the described approaches.

Data analysis

Pre-operative variables included age, gender, body mass index (BMI), localization of the primary colon cancer, metachronous or synchronous CRCLM, mucinous histological subtype, gene testing in particular *RAS* and *BRAF* mutation, carcinoembryonic antigen (CEA) level at the colorectal diagnosis and before hepatic surgery, chemotherapy regimen, American Society of Anesthesiologists (ASA) score and Eastern cooperative oncology group performance status (ECOG PS). Perioperative data included combined surgery (removal of the primary tumor plus liver surgery) rate, bilobar lesions rate, segments involved, hepatic burden, operative time, and intra-operative complications. Post-operative short-term data included hospital stay, post-operative complications also expressed by Clavien-Dindo classification (7), and 30-day mortality rate. Follow-up information were obtained by clinical examination and radiological imaging and included Relapse-free Survival (RFS) and post-resection Overall Survival (OS). Moreover, any further hepatic recurrence and reiterated surgical treatments were recorded and evaluated. All patients have been followed up by oncologists and discussed by an appropriate multidisciplinary team.

Statistical analysis

For data analysis, the Chi-square test was used to define associations between categorical factors and surgical groups. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using the ANOVA test. Variables with abnormal distribution were expressed as median and compared using the Kruskal- Wallis Test. Survival was compared using Kaplan–Meier curves and log-rank test. Univariate analyses were performed to determine which variables were associated with postoperative mortality and survival; the variables with a p-value <0.1 at the univariate analysis were subjected to multivariate analysis using the Cox regression method and the results were provided in terms of hazard ratio (HR). A p-value ≤ 0.05 was considered statistically significant. The statistical analysis was performed using SPSS (Statistical Production and Service Solution for Windows, SPSS Inc., Chicago, IL, USA), version 24.

Results

From December 2014 to December 2021, 104 patients underwent hepatic surgery with curative intent for CRCLM at our tertiary center and met the inclusion criteria of the study. From this pool, we extracted the one-to one case-matched study sample consisting in 20 patients for SURG+IMW group and 20 patients for SURG group.

Patients' characteristics for each group are summarized in Table 1, showing similar baseline features, except for a trend towards a higher rate of synchronous treatment of the primary tumor in the SURG+IMW group (90% vs 65%, p=0.058). In particular, in SURG+IMW group hepatic clearance was

combined with primary colon resection in eight cases: two right hemicolectomies, three sigmoidectomies and three anterior rectal resections were performed, whereas in the SURG group we contextually performed three right hemicolectomies, one sigmoidectomy and one anterior rectal resection (p=0.311). Fifteen patients in SURG+IMW group and fourteen patients in the SURG group received systemic treatment before surgery (p=0.925). In particular, most of the patients had received chemotherapy (triplet or doublets) in association with biologic agents. Bilobar distribution of metastases was observed in 30% of patients in SURG+IMW group vs 55% in SURG group, p= 0.110), and more than five segments involved were found in 15% of patients in SURG +IMW group vs 10% in SURG group, p= 0.633), without significant differences between the two groups.

Intra-operative data are expressed in Table 2. Operative time was 299.4 ± 92.1 min in SURG+IMW group vs 252.4 ± 78.1 min in SURG group (p=0.09). No differences were found between the two groups in of overall complications rate and their severity according to the Clavien-Dindo classification (p=0.225), as well as in mean hospital stay: 9.8 ± 3.3 days for SURG+IMW group vs 13.7 ± 12.4 days for SURG group (p=0.187). No patient required a re-intervention in the post-operative period. In-hospital mortality was registered in one patient of the SURG group who died 27 days after hepatic resection combined with anterior rectal resection, due to sepsis and hepatic failure.

The mean follow-up was 26.0 ± 19.6 months for SURG +IMW group and 18.9 ± 16.0 months for SURG group (p=0.220) (Table 3). No significant difference was found in terms of RFS: median RFS was 9.5 months (4.8 – 14.2) for the SURG+IMW group and 2.4 months (0 – 6.3) for the SURG group (HR 1.2; 95% CI 0.56-2.4; p=0.685). No difference was reported between the two groups in terms of post-resection OS: median OS was 53.0 months (39.9 – 66.1) for the SURG+IMW group and 32.5 months (16.7 – 48.2) for the SURG group (HR 2.13; 95% CI 0.74-6.09; p=0.151) (Figure 1, Figure 2).

Twelve patients (60%) in SURG+IMW group and thirteen patients (65%) in SURG group experienced hepatic recurrence after curative treatment (p=0.774). Among them, 7/12 (58.3%) patients of SURG+IMW group and 7/13 (53.7%) patients of SURG group underwent at least one further surgical treatment (p = 1.000). None of them had recurrence at the same surgical or ablation site of the first hepatic treatment.

In univariate analysis, ECOG PS (HR 2.03; 95% CI 0.99-4.18; p=0.054) was significantly associated with shorter RFS, whereas mucinous histology (HR 2.972, 95% CI 0.914-9.667, p=0.07) and ECOG PS (HR 3.344, 95% CI 1.072-10.430, p=0.038) were associated with a reduced post-operative OS.

In the multivariate model, the ECOG PS (HR 4.959; 95% CI 1.385-17.775; p=0.014) and mucinous histology (HR4.113; 95% CI 1.161-14.573; p=0.028) remained significant predictor of post-operative OS (Table 4).

TABLE 1 Pre-operative data.

	SURG+IMW-group(n=20)	SURG-group(n=20)	p value
Age (years), mean ± SD	64.7±11.4	65.7±13.8	0.794
Male: Female, n (%)	10:10 (50.0:50.0)	11:9 (55.5:45.5)	0.752
BMI (kg/m2), mean ± SD	24.7±4.5	25.0±3.0	0.808
Right colon: Left colon, n (%)	6:14 (30.0:70.0)	7:13 (35.0:65.0)	0.736
Metachronous: Synchronous, n (%)	2:18 (10.0:90.0)	7:13(35.0:65.0)	0.058
Mucinous cancer, n (%)	5 (25.0)	6 (30.0)	0.723
Gene testing, n (%)			0.620
Wild type (WT)	10 (50.0)	11 (57.9)	
RAS mutation	9 (45.0)	6 (31.6)	
BRAF mutation	1 (5.0)	2 (10.5)	
MSS: MSI, n (%)	19:1 (95.0:5.0)	19:1(95.0:5.0)	1.000
CEA level at diagnosis < 5 ng/mL, n (%)	3:11 (21.4:78.6)	5:6 (45.5:54.5)	0.201
CEA level pre-surgery < 5 ng/mL, n (%)	6:6 (50.0:50.0)	4:6 (40.0:60.0)	0.639
Systemic treatment before surgery, n (%)	15 (75.0)	14 (70.0)	0.925
ASA score, n (%)			0.726
2	4 (20.0)	6 (30.0)	
3	13 (65.0)	12 (60.0)	
4	3 (15.0)	2 (10.0)	
ECOG PS score, n (%)			1.000
0-1	19 (95.0)	19 (95.0)	
2	1 (5.0)	1 (5.0)	

BMI, Body Mass Index; MSS, Micro-Satellite Stable; MSI, Micro-Satellite Instable; ASA score American Society of Anesthesiologists; ECOG PS score, Eastern cooperative oncology group performance status.

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TABLE 2 Intra-operative data.

	SURG+IMW-group (n=20)	SURG-group (n=20)	p value
Combined surgery, n (%)	8 (40.0)	5 (25.0)	0.311
Bilobar lesions, n (%)	6 (30.0)	11 (55.0)	0.110
Segments involved > 5, n (%)	3 (15.0)	2 (10.0)	0.633
Hepatic Burden			1.000
Low (1-3 lesions, ≤ 3 cm diameter)	3 (15.0)	3 (15.0)	
Intermediate (4-10 lesions, ≤ 5 cm diameter)	12 (60.0)	12 (60.0)	
High (>10 lesions, > 5 cm diameter)	5 (25.0)	5 (25.0)	
Operative time (min), mean ± SD	299.4±92.1	252.4±78.1	0.090
Intra-operative complications, n (%)	0 (0.0)	0 (0.0)	1.00

Focusing on patients who underwent further surgical treatment for CRCLM relapse, in SURG+IMW group 3/7 patients underwent wedge resection, 1/7 underwent wedge resection plus IMW, 1/7 underwent right hepatectomy and 2/7 underwent lateral sectionectomy. One of the patients treated with wedge resection needs a further surgical hepatic clearance for recurrence 10 months later. Among these 7 patients, 2 (28.5%) are still alive with a mean follow up of 31.7 months. In SURG group 7/7 patients underwent wedge resection; three of them (42.8%) are still alive with a mean follow up of 50.0 months.

Discussion

The surgical treatment of CRCLM in combination with systemic therapies is continuously evolving, leading to a great improvement of oncological outcomes of patients, and even to cure a subgroup of them. Several approaches have been described with the intent of tumor eradication without compromising liver function. Firstly, major hepatectomies and their variants such as portal vein embolization or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) were widely performed, posing their rationale in an aggressive curative anatomical resection with safe resection margins (8). However, these procedures are characterized by high morbidity and possible tumor progression during the interval period, so that nowadays their indication is much more restricted.

In this scenario, PSS has progressively gained popularity, based on the principle that CRCLM are a systemic disease for which surgery represents an important step of the treatment, but the major address must be organ preservation for further

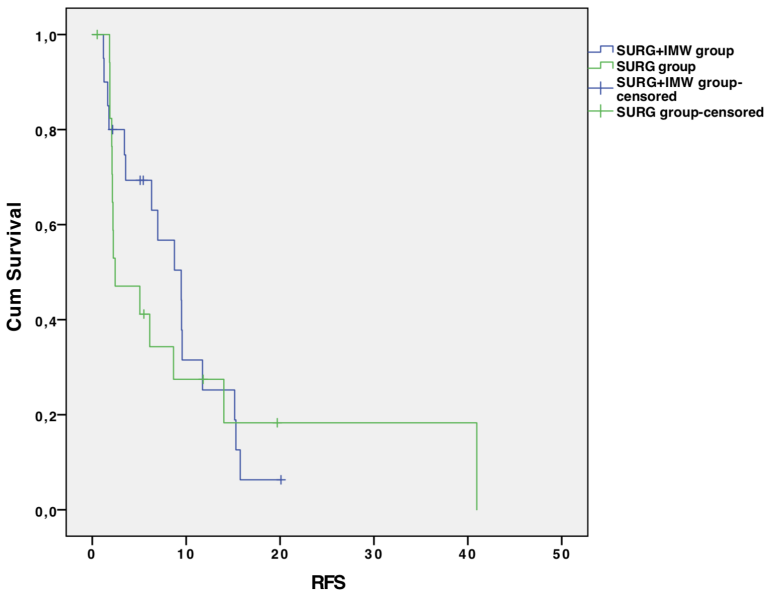

FIGURE 1
Disease-free survival in the two groups.

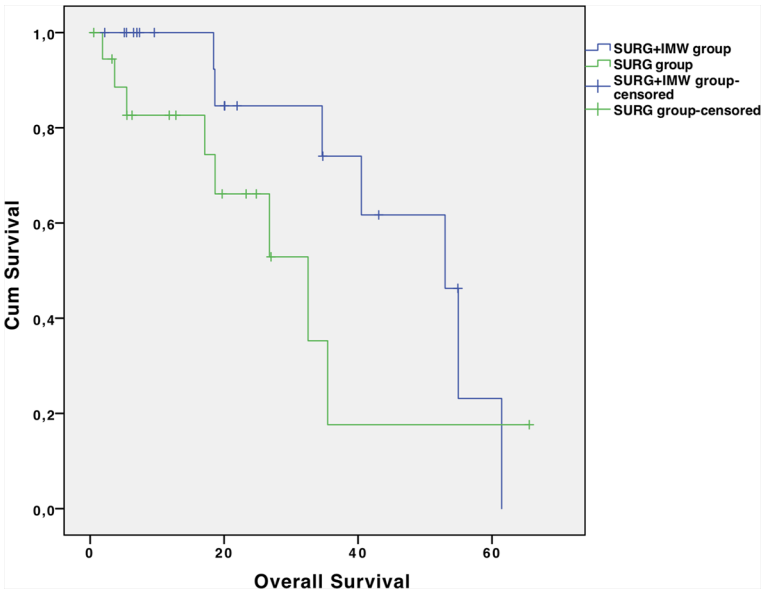

FIGURE 2
Overall survival in the two groups.

therapies. In fact, this approach can be combined with early systemic treatments and can be also adopted to treat hepatic recurrences which are estimated to affect half of patients within two years after surgery. Several studies have reported on PSS demonstrating better results in terms of postoperative complications and liver function preservation respect to major hepatectomies, while ensuring similar oncological outcomes, thus becoming the surgical treatment of choice for patients with CRCLM (3, 9, 10). However, if PSS is safe and quite simple for superficial lesions, it can become more challenging in case of deeper metastases. Moreover, a high hepatic burden of disease poses some drawbacks related to a possible increase of blood loss, a potential sacrifice of a disproportionate amount of parenchyma respect to the size of the lesion, and surely to a prolonged operative time, all factors that may affect the surgical outcomes. In this scenario with the reported lower morbidity

TABLE 3 Post-operative data.

	SURG+IMW-group (n=20)	SURG-group (n=20)	p value
Post-operative complications, n (%)	9 (45.0)	14 (70.0)	0.110
Clavien- Dindo grading, n (%)			0.225
0	11 (55.0)	6 (30.0)	
1	1 (5.0)	0 (0.0)	
2	7 (35.0)	11 (55.0)	
3	1 (5.0)	3 (15.0)	
Hospital stays (days), mean ± SD	9.8±3.3	13.7±12.4	0.187
30-days mortality, n (%)	0 (0.0)	1 (5.0)	0.311
Follow up (months), mean ± SD	26.0±19.6	18.9±16.0	0.220
PD post-surgery, n (%)	16 (80.0)	14 (73.7)	0.640
Hepatic recurrence, n (%)	12 (60.0)	13 (65.0)	0.744
Repeat liver resection for recurrence, n (%)	7 (35.0)	7 (35.0)	1.000
RFS (months), median (range)	9.5 (4.8 – 14.2)	2.4 (0 – 6.3)	0.685
OS (months), median (range)	53.0 (39.9 – 66.1)	32.5 (16.7 – 48.2)	0.151

PD, Progression Disease; RFS, Relapse Free survival; OS, Overall Survival.

TABLE 4A Univariate and multivariate analysis for OS.

	Univariate Analysis OS			Multivariate Analysis OS		
	p	HR	95% CI	p	HR	95% CI
Surg+IMW vs surgery	0.159	2.128	0.744-6.090			
Right colon vs Left colon	0.840	1.114	0.391-3.169			
Metachronous vs Synchronous	0.511	0.582	0.115-2.930			
Mucinous cancer	**0.070**	2.972	0.914-9.667	**0.028**	4.113	1.161-14.573
WT vs RAS	0.553	1.424	0.443-4.581			
WT vs BRAF	0.783	0.744	0.091-6.106			
MSS vs MSI	0.535	0.043	0.000-895.567			
CEA level at diagnosis < 5 ng/mL	0.851	1.124	0.333-3.789			
CEA level pre-surgery < 5 ng/mL	0.480	0.595	0.141-2.590			
Systemic treatment before surgery	0.146	4.575	0.590-35.459			
ECOG PS score	**0.038**	3.344	1.072-10.430	**0.014**	4.959	1.385-17.775
Bilobar lesions	0.763	1.171	0.420-3.263			

Bold values are statistically significant at univariate and multivariate analysis.

coming from literature (11) intra-operative thermal ablation could play a positive role, representing an appealing alternative option to treat deep-located metastases.

Several studies have described the safety and the potential utility of radiofrequency for CRCLM treatment, but when compared to the surgical approach, it has shown inferior results in terms of survival, either alone or in combination with surgery therefore leading to consider this choice as a fallback, and mostly with palliative intent (4, 6, 11, 12). These findings may be related to the intrinsic limits of the radiofrequency, such as the long time required for each thermo-ablation and the limited size of the of the treated area, that can be surpassed with microwaves.

Confirming this, a recent systematic review (13), concluded that MW ablation for lesions smaller than 3 cm represents a safe and valid option of treatment with curative intent for selected patients with CRCLM, therefore overcoming the widespread concept among surgeons of a less oncological radicality with this alternative approach, at least in selected patients.

However, although this specific ablation technique has been available since twenty years, only few papers have dealt with it in combination with surgery so far (14, 15), and most of them are affected by several bias related to the type of MW device used (mostly currently surpassed), to the heterogeneity of the sample, to the absence of a control group, or to the lack of an oncologic follow-up. This consideration prompted us to review our experience in this field, with a particular attention to the oncological outcomes.

To the best of our knowledge, the present work is the first one that compares surgery plus IMW versus surgery alone with

TABLE 4B Univariate and multivariate analysis for RFS.

	Univariate Analysis DFS		
	p	HR	95% CI
Surg+IMW vs surgery	0.685	1.165	0.557-2.437
Right colon vs Left colon	0.505	0.769	0.356-1.663
Metachronous vs Synchronous	0.382	0.688	0.297-1.592
Mucinous cancer	0.428	1.318	0.621-3.072
WT vs RAS	0.282	1.521	0.709-3.264
WT vs BRAF	0.361	2.062	0.436-9.757
MSS vs MSI	0.347	0.042	0.000-31.475
CEA level at diagnosis < 5 ng/mL	0.855	1.090	0.431-2.758
CEA level pre-surgery < 5 ng/mL	0.925	0.953	0.350-2.596
Systemic treatment before surgery	0.992	1.004	0.426-2.366
ECOG PS score	**0.054**	2.032	0.987-4.182
Bilobar lesions	0.307	0.674	0.316-1.436

an updated ablation system for the treatment of patients, with the same burden of CRCLM, up to 40 mm for each lesion, using a case match methodology, and with a mid-term oncologic follow-up evaluation.

In our series, similarly, to the peri-operative data, the mid-term survival results were not significantly different between the two groups, and most importantly, the type of intervention did not influence these parameters neither in the univariate nor in the multivariate analysis. Moreover, following our imaging revision, in case of hepatic recurrence, the second relapse did not interest the first surgical or IMW site, reinforcing the concept of efficacy of both treatments.

Hence, our results support that the decision to perform an IMW ablation does not increase the peri-operative morbidity, and does not negatively influence the post-operative survival and the risk of relapse, and therefore should be considered only a technical surgeon's choice. Indeed, since comparing the same burden of disease we did not register differences in OS and RFS between the two groups, the surgeon should be aware that choosing to treat a small (up to 40 mm), deep metastasis difficult to be removed with MW ablation could be preferable to a more aggressive surgery, as the survival will be not affected by this choice. Instead, in these cases, particularly when facing with multiple metastases, a radical surgery alone is likely to be affected by higher operative times, blood loss, morbidity and mortality, or oblige to an unnecessary liver parenchyma sacrifice.

In this regard, because of its retrospective nature, our series has the limitation that, although the two groups of patients had similar burden of disease and operative risk, the location of the lesions and the surgical complexity of their resection were not exactly comparable and therefore, unlike the oncologic outcomes, the results of surgical outcomes were less meaningful. Nevertheless, although not statistically significant, we registered a trend towards a lower rate of complications and reduced hospitalization in the SURG+IMW group, in line with the propensity score analysis conducted by Xourafas et al. (15) that showed reduced morbidity and length of hospital stay in patients treated with surgery and intra-operative thermal ablation. These results could also be explained by the intuitive observation that in SURG+IMW approach the treatment of deep CRCLM was faster and characterized by a lower parenchymal deep dissection. Another point in favor of IMW ablation is its particularly quick application as, unlike RF which ablation time ranges from 20 to 30 minute for every single lesion, the ablation time of IMW ranges from 2 to 5 minute, therefore allowing multiple treatments without being excessively time consuming. This aspect in our experience has revealed to be particularly important in the treatment of multiple CRCLM, allowing to resect up to 25 superficial metastases and to thermo-ablate up to 26 deep ones in a single patient. Instead, the trend towards a longer operative time registered in SURG+IMW group is probably related to the significantly higher rate of combined interventions (hepatic plus primary cancer resection) in this group.

Thanks to innovations in surgical and ablation techniques and more effective systemic therapeutic regimens and the fundamental role of a multidisciplinary management, the survival of patients with CRCLM is becoming longer and longer, even in case of recurrence, so that oncologists and surgeons are now dealing with a "chronic disease" (16). Surgical resection for second hepatic relapse has been reported to be associated with surgical risk and long-term outcomes similar to those of the first hepatic resection, with a 5-year OS rate ranging from 27 to 45% (17). Only few papers have reported similar results with thermal-ablation in CRCLM recurrences (18). In our study, although surgery was the most used approach for hepatic recurrences, patients who underwent further IMW ablation showed good results, underlining its role as a radical option also in this setting.

Main limitations of the study are the monocentric and retrospective nature, as well as the possible oncologic selection bias related to exclusion of prognostic criteria (i.e., ECOG-PS, *RAS* and *BRAF* mutational status, time to presentation of liver metastases) from matching approach due to small sample size. However, no significant differences were observed between SURG+IMW and SURG groups in terms of prognostic parameters. The limited number of patients included in the study is a relevant shortcoming, but we choose to give more importance to comparability respect to statistical power and therefore we tried to mitigate these limitations by matching patients for hepatic burden of disease and for surgical risk, with the main aim to give indication on the oncological results. Moreover, another limitation could be related to the estimation of hepatic tumor burden as this is another matter of debate with several scores adopted for the evaluation of liver disease load (19, 20). Finally, we included patients enrolled in a long period in which the patient's selection had undergone important improvements in order to refine the choice of systemic treatment with considerable impact in terms of clinical outcome. While the two cohorts shared homogeneous baseline characteristics, overall population of our work included a diversified spectrum of colon liver metastases patients (resecatable, potentially resectable or initially unresectable) who have received different pre-surgery therapies thus making findings hardly comparable with available data from literature in terms of RFS and OS. After resection of colorectal liver metastases with curative intent, a recent comparative analysis reported a minimal correlation between RFS and OS (21) showing a wide range of time intervals from recurrence to death, thus limiting the value of RFS as a surrogate endpoint for OS. This assumption together with the recent evolution of locoregional and surgical techniques for second hepatic relapse

and the availability of active systemic treatments can explain our results in terms of OS.

In conclusion, data emerged from the present case matched series support the use of IMW in association with surgery for the treatment of CRCLM, also in case of hepatic relapse. This approach seems to be not inferior to resection alone in selected patients, and may be particularly indicated in those who have small multiple and deep-located metastases in which we can predict a difficult and time-consuming surgery. IMW ablation should not be considered a worse alternative to surgical resection in patient with multiple CRCLM, but an integrated treatment in a parenchymal sparing approach in which we should balance oncologic outcomes and patient's safety. This approach could also be used in patients with CRCLM relapse who have already undergone hepatic surgery. Further studies are needed to be more conclusive on the role of IMW ablation in this setting (22).

Data availability statement

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

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

Author contributions

Study concepts: SG, NF, MP, LM, CC. Study design: MC, GD, AC, NF, GF, SG, FM. Data acquisition: MC, GD, AC, DG, RM, SG, FM. Quality control of data and algorithms: SG, FM, GF, EC, GC, LM. Data analysis and interpretation: GF, SG, FM, MP, EC, GM. Statistical analysis: GF, SG, FM, GD, EC, LM. Manuscript preparation: SG, FM, LM, CC, RM, DG. Manuscript editing: SG, FM, LM, CC, GC, RM, GM. Manuscript review: SG, FM, LM, CC, GC, RM, GM. 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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