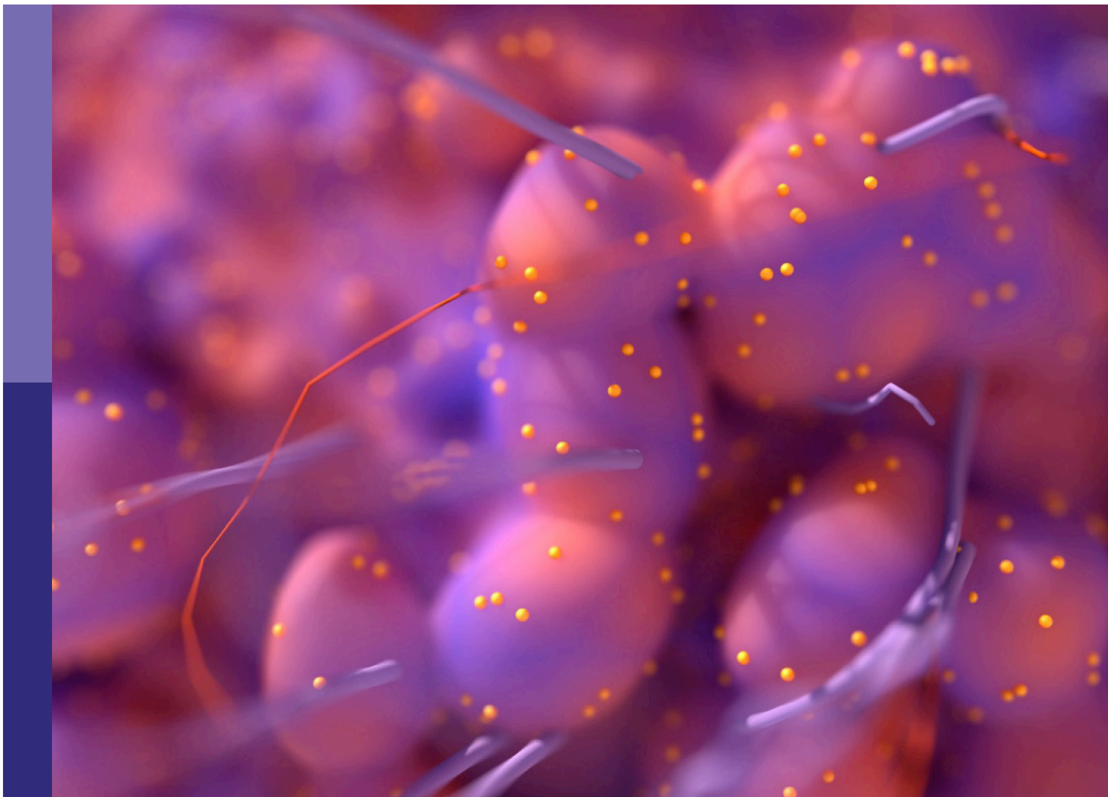
Frontiers | Research Topics

Surgical oncology in the elderly: The state of the art and future challenges

Edited by
Cosimo Sperti, Lucia Moletta and Felix Berlth

Published in
Frontiers in Oncology
Frontiers in Surgery



ISSN 1664-8714
ISBN 978-2-8325-2843-3
DOI 10.3389/978-2-8325-2843-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Surgical oncology in the elderly: The state of the art and future challenges

Topic editors
Cosimo Sperti — University of Padua, Italy
Lucia Moletta — University of Padua, Italy
Felix Berlth — University Medical Centre, Johannes Gutenberg University Mainz, Germany

Citation
Sperti, C., Moletta, L., Berlth, F., eds. (2023). *Surgical oncology in the elderly: The state of the art and future challenges*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-2843-3

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 13 June 2023
DOI 10.3389/fonc.2023.1224278

Check for updates

OPEN ACCESS

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

*CORRESPONDENCE
Cosimo Sperti
csperti@libero.it

RECEIVED 17 May 2023
ACCEPTED 06 June 2023
PUBLISHED 13 June 2023

CITATION
Sperti C, Moletta L and Berlth F (2023) Editorial: Surgical oncology in the elderly: the state of the art and future challenges. *Front. Oncol.* 13:1224278.
doi: 10.3389/fonc.2023.1224278

Editorial: Surgical oncology in the elderly: the state of the art and future challenges

Cosimo Sperti[1]*, Lucia Moletta[2] and Felix Berlth[3]

[1]Department of Surgery, Oncology and Gastroenterology, Hepato-Bilio-Pancreatic (HPB) Unit, University of Padua, Padova, Italy, [2]Department of Surgery, Oncology and Gastroenterology, 1st Surgical Clinic, University of Padua, Padova, Italy, [3]Mainz University, Johannes Gutenberg Universitat Mainz, Mainz, Germany

KEYWORDS

surgical oncology, elderly, esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer

Editorial on the Research Topic
Surgical oncology in the elderly: the state of the art and future challenges

The number of old patients with cancer is increasing since population ageing is a common event throughout the world. It is estimated that the number of persons aged 80 years or over increase more than threefold between 2017 and 2050, rising from 137 million to 425 million (1). So, more elderly patients with cancer requiring a surgical evaluation are expected in clinical practice. However, surgical oncology in the elderly presents several problems. Undoubtedly, the decline in physiological systems and the presence of comorbidities have an impact in the surgical management of cancer patients together with the tolerance to oncological treatments (2). Moreover, we are lacking clear evidence-based informations about this topic because only small subset of geriatric cancer patients has been included into clinical trials (3).

The surgical management of elderly patients with cancer is still a challenge and frequently troubles the surgeon. The current problem is the preoperative assessment of elderly patients and the search for prognostic factors suggestive for frailty or other factors influencing perioperative outcome (4). The role of age as prognostic index in old patients undergoing surgical treatment shows contrasting results. Some studies reported age as an independent prognostic factor for morbidity and mortality after surgery, while other Authors have suggested that elderly patients with healthy conditions are candidate for surgical resection with the same surgical risk of younger patients (5, 6).

Another problem is the feasibility of multimodality therapy (neoadjuvant or adjuvant therapy) in such elderly patients. Toxicity of chemotherapy and/or radiotherapy regimens may be increased in geriatric patients and limited physiological reserve make difficult to complete oncological treatments (7). Finally, the role of minimally invasive surgical resections in the elderly remains to be assessed (8).

Within this Research Topic, the manuscript by Hu et al. reports a successful laparoscopic resection of two malignancies (left hepatectomy and total hysterectomy) in a 75-year-old woman with intrahepatic cholangiocarcinoma and endometrial cancer, emphasizing that laparoscopic complex operation may be offered to elderly, well-selected patients.

The work of Jin et al. focused on the impact of malnutrition on outcome after major surgical procedures for cancer. The Authors showed that Protein-Energy Malnutrition (PEM) was associated with increased risk of mortality, major complications, higher total cost, and longer length of stay.

The paper by Zhang et al. analyzed the local treatment of ductal carcinoma *in situ* (DCIS), including breast surgery, axillary lymph node (ALN) surgery, and radiotherapy in different subgroups of aged patients. Associations with clinicopathological findings and outcome after surgery were evaluated. Age and tumor size were independent factors influencing the breast and ALN surgery. Compared with patients aging 60-69, octogenarian patients underwent more breast conserving surgery (BCS) and less ALN surgery. Age was the only factor associated with the radiotherapy decision after BCS in elderly patients with DCIS.

Gallina et al. reported their experience of robotic pulmonary lobectomy in a population of 103 patients older than 75 years. Thirty-five patients reported postoperative complications without mortality. The factors that could predict the complication rate were the predicted postoperative FEV1 and the nodal disease. The Authors outlined that the predicted postoperative FEV1 and the preoperative staging should be carefully evaluated in order to improve postoperative outcome.

The value of minimally invasive surgery in elderly patients has been reported by Capovilla et al. In two high-volume centers from Italy and Germany, 160 patients older than 75 years underwent open (n=102), laparoscopic (MIE; n=249) or robotic (RAMIE; n=34) esophagectomy. Among elderly patients MIE/RAMIE were significantly associated with a lower overall morbidity, less pulmonary complications and a shorter hospital stay.

Xu et al. evaluated the effect of surgery for gallbladder cancer in elderly patients (> 70 years). Patients with surgery had significantly longer overall survival (OS) and cancer-specific survival (CSS) than those without surgery, especially patients aged 70-84 years old. An age >85 years was significantly associated with poor OS and CSS.

The morbidity and mortality after gastrectomy for gastric or distal esophageal cancer in patients aged >75 years in Germany, are presented in the work of Berlet et al. In a total of 67389 gastrectomized patients, the rate of patients aged 75 years or older was 51.4%. The hospital mortality of elderly patients was significantly higher, as well as the general complications and the need for resuscitation. Systematic D2 dissection, peritonectomy and hyperthermic intraperitoneal chemotherapy were less frequently performed in older patients compared to the younger countpart.

The paper by Bao et al. evaluated 144 patients who underwent surgical resection following nCRT for mid-low rectal cancer. The correlations between BMI and radiologic fat parameters with pathologic response and survival were investigated, without showing any difference in terms of OS and disease -free survival. Age did not correlate with pathologic response or survival.

Correlation between age and postoperative outcome in colorectal cancer patients was investigated by (Turri et al.) In a large cohort of 1482 patients operated for colorectal cancer, postoperative mortality was low in octogenarians (3.2%). OS decreased with advancing age. Although the results of surgery in elderly patients were acceptable, OS is strongly dependent on age. Compared to younger patients, mortality in older people was frequently due to competing causes rather than to cancer-related managements.

In order to better identify the prognostic factors in elderly operated for colorectal cancer, Mao and Lan performed a systematic review and meta-analysis on the prognostic value of the Geriatric Nutritional Risk Index (GNRI). The study included ten reports for a total of 3802 patients. Meta-analysis showed a significant poor overall survival (and disease-free survival) and higher risk of complications in patients with low GNR1. When a subgroup analysis based on age was performed, the results did not change.

In conclusion, all contributions to this Research Topic suggest that major cancer surgery may be safe and feasible in elderly patients, but the risk of postoperative complications undoubtedly exists and worries surgeons and oncologists. Despite oncological outcome appears not influenced by patients' age, we have few informations about the quality of life of these patients. Future studies are needed to identify simple indicators to stratify patients for more precise surgical risk and formulate personalized treatment plans.

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.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. In: *World population ageing 2017 – highlights (ST/ESA/SER.A/397).*

2. Maltser S, Cristian A, Silver JK, Morris GS, Stout NL. A focused review of safety considerations in cancer rehabilitation. . *PM R* (2017) 9(9S2):S415–28. doi: 10.1016/j.pmrj.2017.08.403

3. Sedrak MS, Freedman RA, Cohen HJ, Muss HB, Jatoi A, Klepin HD, et al. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. *CA Cancer J Clin* (2021) 71(1):78–92. doi: 10.3322/caac.21638

4. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc* (2008) 56(12):2211–16. doi: 10.1111/j.1532-5415.2008.02008.x

5. Taylor JC, Iversen LH, Burke D, Finan PJ, Howell S, Pedersen L, et al. Influence of age on surgical treatment and postoperative outcomes of patients with colorectal cancer in Denmark and Yorkshire, England. *Colorectal Dis* (2021) 23(12):3152–61. doi: 10.1111/codi.15910

6. Cheng YX, Liu XY, Kang B, Tao W, Wei ZQ, Peng D. Comparison of surgical and oncologic outcomes in very elderly patients (≥ 80 years old) and elderly (65-79 years old) colorectal cancer patients: a propensity score matching. *BMC Gastroenterol* (2022) 22(1):205. doi: 10.1186/s12876-022-02277-y

7. Feliu J, Jiménez-Munárriz B, Basterretxea L, Paredero I, Llabrés E, Antonio-Rebollo M, et al. Predicting chemotherapy toxicity in older patients with cancer: a multicenter prospective study. *Oncologist*. (2020) 25(10):e1516–24. doi: 10.1634/theoncologist.2019-0701

8. Ngu JC, Kuo LJ, Teo NZ. Minimally invasive surgery in the geriatric patient with colon cancer. *J Gastrointest Oncol* (2020) 11(3):540–4. doi: 10.21037/jgo.2020.02.02

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 29 July 2022
DOI 10.3389/fonc.2022.916104

Check for updates

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Luca Saadeh,
University Hospital of Padua, Italy
Michele Valmasoni,
Universitàdi Padova, Italy

*CORRESPONDENCE
Kunpeng Hu
hukpeng@mail.sysu.edu.cn
Bo Liu
hkpdhy918@vip.126.com
Jiajia Chen
81718370@qq.com

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

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 08 April 2022
ACCEPTED 07 July 2022
PUBLISHED 29 July 2022

CITATION
Hu K, Ke Y, Chen Q, Wu J, Ke Y, Xie Q, Liu B and Chen J (2022) Case report: dual primary malignancies treated by laparoscopic multiorgan resection with natural orifice specimen extraction surgery.
Front. Oncol. 12:916104.
doi: 10.3389/fonc.2022.916104

Case report: dual primary malignancies treated by laparoscopic multiorgan resection with natural orifice specimen extraction surgery

Kunpeng Hu[1,2*†], Yifan Ke[1†], Qin Chen[2], Jiezhong Wu[1], Yingping Ke[2], Qiuxian Xie[3], Bo Liu[1*] and Jiajia Chen[2*]

[1]Department of General Surgery, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [2]Department of General Surgery, Chaozhou Central Hospital, Chaozhou, China, [3]Department of Gynecology, Chaozhou Central Hospital, Chaozhou, China

With microtrauma becoming a consensus, in order to improve surgical treatment capability, the clinical application of laparoscopic multiorgan resection is becoming more and more complicated and diversified. Recently, we successfully presented a case of transvaginal specimen extraction surgery that included laparoscopic anatomical left hemihepatectomy combined with laparoscopic total hysterectomy and bilateral adnexectomy and the pelvic and para-aortic lymphadenectomy. The patient, a 75-year-old woman, was hospitalized with abnormal vaginal discharge and bleeding. The pathologic diagnosis of uterine curettage was endometrioid adenocarcinoma. After completing examinations such as color Doppler ultrasound, CEUS, MRCP and thoracoabdominal enhanced spiral CT, preoperative diagnosis was considered as endometrial cancer and a space-occupying lesion in the liver (primary or secondary site)?. No lymphatic or distant metastasis had been found. We also excluded Lynch syndrome by digestive endoscopy and gene sequencing. After a multidisciplinary consultation, the patient underwent surgery under general anesthesia on 24 September 2021. The operation was completed uneventfully in 6 hours, then the patient was transferred to the ICU for follow-up monitoring. The patient began to eat and was able to leave bed on the 4th postoperative day. According to immunohistochemistry, the patient's postoperative diagnosis was intrahepatic cholangiocarcinoma (ICC) and endometrial cancer. Compared with open surgery, laparoscopic multiorgan resection with natural orifice specimen extraction surgery (NOSES) has many advantages such as fewer traumas, shorter recovery time, and better postoperative quality of life. However, combined large-scale laparoscopic surgeries of different organs can be challenging for surgeons and anesthesiologists. No similar cases have been searched.

KEYWORDS

natural orifice specimen extraction surgery (NOSES), dual primary malignancies, laparoscopic multiorgan resection, intrahepatic cholangiocarcinoma (ICC), endometrial cancer, case report

Introduction

Endometrial cancer is a type of endometrioid adenocarcinoma that is common in perimenopausal women. In developed countries, endometrial cancer is the most common gynecologic malignancy. The main symptoms are abnormal vaginal bleeding and discharge. Tumor metastasis includes hematogenous dissemination, lymphatic system invasion and direct invasion. Laparoscopic total hysterectomy and bilateral adnexectomy combined with pelvic and para-aortic lymphadenectomy is the standard treatment for endometrial cancer (1).

ICC is a type of adenocarcinoma that originates in the epithelium of secondary bile ducts and its branches. ICC accounts for approximately 10%-15% of primary malignancies in the liver, and the incidence rate has increased in recent years. ICC lacks characteristic symptoms, so its early diagnosis and long-term prognosis are poor. Radical resection is the main treatment for ICC (2).

Although laparoscopic multiorgan resection is challenging, it avoids from the need for repeated surgery and represents a high-level surgical technique. Anatomical hepatectomy refers to the precise removal of the malignancy and the hepatic segments in which it is located anatomically. Compared with nonanatomical hepatectomy, it has advantages in terms of the incidence of postoperative complications and disease-free survival (DFS) (3). However, the prognosis of patients after anatomical hepatectomy also depends on some risk factors such as preoperative cirrhosis and tumor characteristics, so anatomical hepatectomy should be presented as an option for only eligible patients (4). In natural orifice specimen extraction surgery (NOSES), the surgeon does not need to extract specimens by enlarging the incision during laparoscopic surgery; instead, the specimen is extracted through the rectum, anal tube, or vagina. NOSES reduces patient pain and shortens recovery time. Transvaginal specimen extraction surgery is common in gynecological or colorectal surgery (5).

This case report has been reported in line with the SCARE Criteria (6).

Case description

The patient, a 75-year-old woman who comes from Chaozhou, Guangdong, was hospitalized in the Department of Gynecology due to 4 months of abnormal vaginal discharge and 10 days of vaginal bleeding. The patient didn't have any other symptoms. Clinicians didn't find any positive signs on physical examination. And the patient had never received any previous diagnostic examination or treatment. She had hypertension and type 2 diabetes. Both blood pressure and glucose were stably controlled by taking Amlodipine Besylate and Metformin hydrochloride Po Qd. The patient also denied the history of surgery, trauma, blood transfusion, drug allergy, smoking and drinking. Her family members were all healthy, without history of cancer or genetic disease.

The pathologic result of diagnostic uterine curettage was endometrioid adenocarcinoma. However, abdominal color Doppler ultrasound revealed a low echo-level focus in segment IV of the liver with intrahepatic cholangiectasis in the left hepatic lobe. In addition, there were no significant abnormalities in the biliary system, pancreas, spleen, urinary system or double annexa.

To further determine the properties of the liver focus, we also performed MRCP and contrast-enhanced ultrasound (CEUS) in the liver. CEUS indicated that the low echo-level focus was ICC. MRCP revealed a space-occupying lesion that encroached on the hepatic portal and left lobe. To determine the stage of the tumor, we performed thoracoabdominal enhanced spiral CT, and the results were as follows: 1. ICC in segment IV with intrahepatic cholangiectasis, 2. endometrial cancer, 3. chronic inflammation and a nodule in the inferior lobe of the left lung, 4. an increscent lymph node in the mediastinum, and 5. no space-occupying lesions in the extrahepatic biliary system, pancreas, spleen or urinary system.

Since the patient was thought to have two primary malignancies and approximately 50% of women with Lynch syndrome have clinical manifestations of endometrial cancer as initial symptoms (7), she was transferred to the department of general surgery for follow-up diagnosis and treatment. Then, we performed digestive endoscopy to eliminate Lynch syndrome, and the result was chronic superficial gastritis. The patient's serum ferritin was 458.70 μg/L, and her CA199 was 45.15 ku/L. Other serum tumor markers were in the normal range.

In summary, the preoperative diagnosis comprised a space-occupying lesion in the liver, endometrial cancer, hysteromyoma, hypertension and type-2 diabetes. The space-occupying lesion in the liver may be ICC, hepatocellular carcinoma or metastatic carcinoma. We intended to confirm the diagnosis by postoperative pathological examination. No lymphatic or distant metastasis had been found. According to the results of auxiliary examination, the patient's surgeons and gynecologists developed a protocol for transvaginal specimen extraction surgery (NOSES): laparoscopic anatomical left hemihepatectomy combined with laparoscopic total hysterectomy and bilateral adnexectomy and pelvic and para-aortic lymphadenectomy.

Due to the risk of large-scale surgery in older patients, we performed exhaustive preoperative examinations. Fortunately, in addition to slight hypopnea, the functions of other systems and the vital signs were normal. The result of Holter monitor ECG was sinus rhythm with several ventricular premature beats and atrial premature beats. There were no significant abnormalities on cardiac color Doppler ultrasound, spiral CT of the coronary artery or lung function examination. After

10.3389/fonc.2022.916104

multidisciplinary consultation and a complete preoperative evaluation, the surgical protocol was considered feasible.

After adequate preoperative communication and preparation such as abrosia, enema, cross-matching blood test and prophylactic antibiotics, the patient underwent surgery under general anesthesia on 24 September 2021 in Chaozhou central hospital. The chief surgeon and gynecologist were all experienced with more than 15 years of career. The patient was placed in the reverse Trendelenburg's position. All the surgical procedures were performed under laparoscopy. Thin-layer CT-Scan and 3D digital reconstruction guided the surgeons in identifying the anatomic structures of organs during laparoscopic microtrauma surgery (Figure 1), thus accurately determining the excisional range and preserving normal liver tissue as much as possible while achieving a radical cure. With the help of an anesthesiologist who precisely maintained a low central venous pressure, surgeons performed laparoscopic anatomical left hemihepatectomy with little bleeding (8). Subsequently, gynecologists added four trocars and completed the laparoscopic total hysterectomy and bilateral adnexectomy and dissected the pelvic and para-aortic lymph nodes (Figure 2). Finally, the surgeons extracted the surgical specimens completely through the vagina, so that there were only some small stomas in the abdominal wall and no operative incision (Figure 3). The operation was completed uneventfully in 6 hours. The total blood loss was estimated to be 200 ml. The abdominal surgical dressings were dry and clean, without staxis or seepage. The drainage tubes for the hepatorenal recess and the hepatic incisal surface were smooth, and a dark red liquid was discharged. The drainage tube in the pelvic cavity was also smooth, and a reddish liquid was discharged.

After the operation, taking into account the patient's risk factors, such as age, extensive surgery and a long operative time, the patient was transferred to the ICU for follow-up monitoring. The patient received oxygen therapy, fluid replacement, nutritional support, antibiotics, analgesia, acid inhibitor, liver protection and eliminate sputum treatment. The postoperative anal exsufflation time was 3 days. The patient began to eat and was able to leave bed on the 4th postoperative day. Her P/F was low after the surgery. Clinicians considered the cause may be old age, a long operative time and preoperative slight hypopnea. Therefore, the patient's tracheal cannula was removed on the 4th postoperative day. The results of postoperative spiral CT and blood work showed no significant abnormalities. The recovery was uneventful, and the patient was discharged from the hospital on the 10th postoperative day (Figure 4).

Specimens included fragmented hepatic tissue (approximately 18 cm in diameter), gallbladder, complete uterus (approximately 8*7*5 cm), bilateral adnexas and lymph nodes. An incanus area (approximately 3 cm in diameter) could be seen near the hepatic portal of the ligament teres hepatis, with a tough texture and an unclear boundary. The mass (approximately 4 cm in diameter) in the uterine cavity had infiltrated the superficial muscular layer (depth<1/2). Neither tumor was accompanied by lymph node metastasis or nerve and vascular encroachment. According to the results of postoperative pathological examination and immunohistochemistry, the patient's postoperative diagnosis was ICC (pT1aN0M0, stage IA) and endometrial cancer (pT1aN0M0, stage IA). In conclusion, the patient's long-term prognosis is good, and the attained clinical outcomes have achieved the expectations.

Clinicians have followed up the patient since she was discharged from the hospital. The patient's adherence and tolerance are good. She can cooperate with clinicians in postoperative follow-up, and follow our advice on treatment, lifestyle and diet. We perform abdominal spiral CT scan and blood tests including serum tumor markers and the liver function to the patient every 3 months. The results are normal, and the double primary malignancies have not recurred so far. Besides, although the patient underwent extensive surgery, she has never suffered any postoperative complications or adverse events.

Discussion

Old age is one of the predisposing factors for malignancy. Radical resection is the primary treatment for most cancers, but such surgeries are usually extensive and cause great trauma. However, due to the aging of the body, which is prone to a variety of underlying diseases, older patients often have less tolerance for surgery (9). Although many of them have surgical indications, they are unable to receive surgery because of their poor physical condition and have to opt for nonradical therapies. Therefore, ensuring a radical cure while minimizing trauma is always a problem for the surgical treatment of cancers.

Recently, due to advances in minimally invasive surgical technology and perioperative support treatment, some surgical contraindications are no longer a problem. However, some intractable cases, such as malignancy with distant metastasis or multiple primary cancers *in vivo*, remain a major challenge for surgeons (10). For example, a conventional laparotomy may be accompanied by with enormous trauma and high mortality. A series of asynchronous laparoscopic resections not only lengthen the treatment cycle but also cause the patient to suffer unnecessary pain, so it is not worth the risk. In contrast, although simultaneous laparoscopic multiorgan resection is more difficult and has a higher risk of conversion to laparotomy, this is still the best choice if appropriate techniques and equipment are used (11, 12).

NOSES is a new technology that supports the trend of minimally invasive surgery. This means that surgeons do not need to extract specimens by enlarging incisions during the course of laparoscopic surgery. NOSES is common in gynecological and colorectal surgery and has extensive applications in other surgical fields (13, 14). Although there was a case of laparoscopic hepatectomy with transvaginal

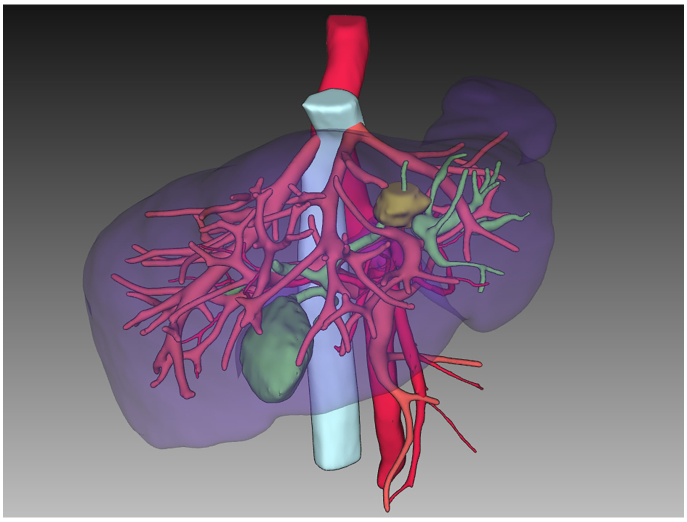


FIGURE 1
The preoperative 3D-restruction of liver.

specimen extraction surgery in 2008 (15), no case of NOSES combined with laparoscopic hepatectomy and total hysterectomy and bilateral adnexectomy has been reported. NOSES prevents postoperative and incision-related complications, reduces postoperative pain, and achieves better abdominal cosmetic results (16). However, all NOSES procedures are performed under laparoscopy, and there are potential risk factors, such as peritoneal infection and tumor cell peritoneal seeding (17). Therefore, NOSES requires excellent surgical techniques and a long operative time.

Multiple primary malignancies are often considered to be caused by a hereditary neoplastic syndrome (e.g., Lynch syndrome) (18). In addition, other risk factors (e.g., old age, tobacco, alcohol, work environment, and genetic mutations) can also make cancer patients susceptible to a synchronous or metachronous second primary malignancy (19). In this case,

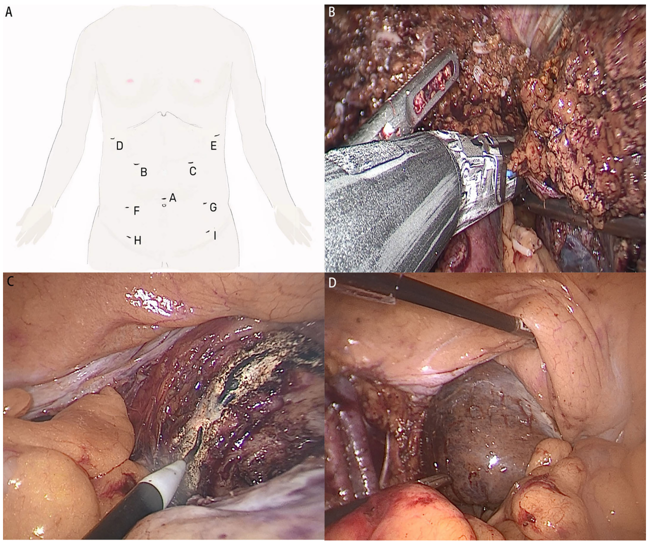


FIGURE 2
(A) Trocars during the operation. **(B)** Resect the left hepatic vein and lobe. **(C)** Cut off the vaginal wall and extract uterus. **(D)** Extract liver specimens through the vagina.

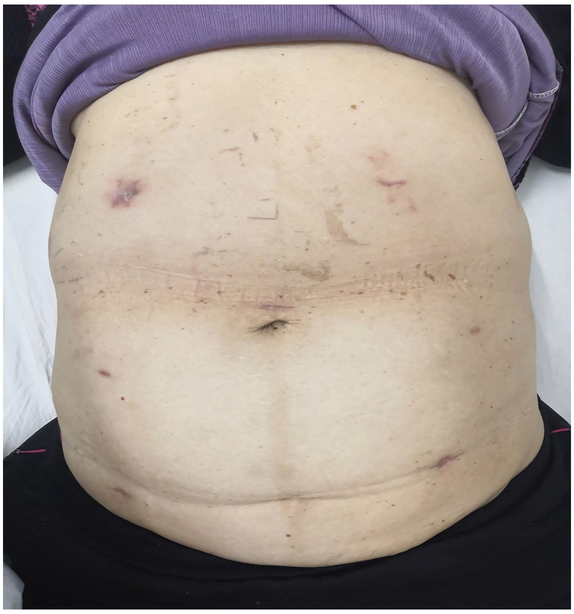


FIGURE 3
The patient's abdomen after dermal sutures out.

an elderly patient synchronously suffered from endometrial cancer and ICC. Lynch syndrome was ruled out through digestive endoscopy and gene sequencing. We found reports of ICC (20) or endometrial cancer (18) with colorectal cancer, but ICC with endometrial cancer has not been reported. Although multiple primary malignancies are rare, the prognosis is poor, and the incidence is gradually increasing (21). Therefore, timely and accurate diagnosis is essential for the treatment and prognosis of such patients. They often receive chemical or targeted therapy (22), but surgical treatment has the advantage of a radical cure, so early multiple primary malignancies should be resected *via* surgery (23). In this case, we developed a complicated and unprecedented NOSES protocol that included high-level surgeries in different departments. In 2015, surgeons performed combined Da Vinci robot-assisted laparoscopic left hepatectomy and total hysterectomy in India (24). In contrast, we creatively chose transvaginal specimen extraction surgery to minimize trauma while ensuring a radical cure.

Microtrauma and radical cure are the two key words for the surgical treatment of cancers, and anatomical hepatectomy and NOSES epitomize these two points. The challenges and benefits of surgery should both be considered. Such complicated surgeries can radically cure refractory malignancy and lower the surgical threshold for older and infirm patients. For this purpose, high-quality hospitals with skilled surgeons and advanced equipment should enable these complicated operations for the benefit of patients. However, such complicated operations are inappropriate for promotion in primary hospitals as this will increase the incidence of surgical complications and adverse events.

In summary, the success of this case shows that the surgical protocols for patients with refractory malignancies should be elaborate and personalized. In cases of refractory malignancy, surgeons should consider the difficulty and risk of surgery, and do all they can to achieve a radical cure while ensuring patients' postoperative quality of life to maximize patient benefits.

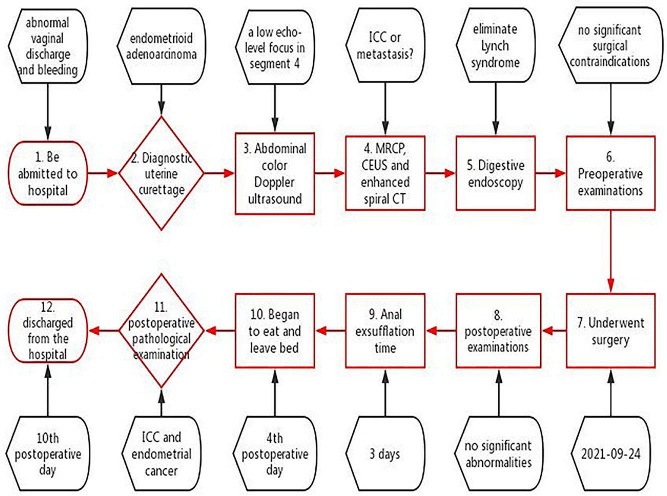


FIGURE 4
Information of care organized as a timeline.

The patient's perspective

I'm very grateful to Dr. Hu and his team for their loving care. Though I had the option to receive radical surgery, cancer and surgery both frightened me. Fortunately, the surgical protocol designed by Dr. Hu's team was satisfactory. It was a minimally invasive surgery, which means they didn't have to make a huge incision on my abdominal wall. And I needn't undergo a revision surgery. So, I received surgery on 24 September 2021. It was completed successfully. Postoperative recovery was uneventful. No complications or cancer recurrence has occurred so far. I'm satisfied with my postoperative quality of life.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article

Author contributions

KH: protocol development, surgical operator and manuscript revision. YFK: data collection and manuscript writing. QC: surgical assistant and clinical follow-up. JW: surgical assistant. YPK: clinical follow-up. QX: operator of gynecological surgery. BL: surgical direction. JC: project assistant and imaging data collection. All authors contributed to the article and approved the submitted version.

Funding

Natural Science Foundation of Guangdong Province of China (2021A15150124), Medical Scientific Research Foundation of Guangdong Province (A2021099), Scientific Research Project of Dongguan Binhaiwan Central Hospital (2021001).

Acknowledgments

The authors thanks Dr. Zhen Xu for his help in this article.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. *Lancet* (2016) 387(10023):1094–108. doi: 10.1016/S0140-6736(15)00130-0

2. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* (2018) 15(2):95–111. doi: 10.1038/nrclinonc.2017.157

3. Moris D, Tsilimigras DI, Kostakis ID, Ntanasis-Stathopoulos I, Shah KN, Felekouras E, et al. Anatomic versus non-anatomic resection for hepatocellular carcinoma: A systematic review and meta-analysis. *Eur J Surg Oncol* (2018) 44 (7):927–38. doi: 10.1016/j.ejso.2018.04.018

4. Tian YL, Ji JJ, Chen LN, Cui XL, Liu ST, Mao L, et al. Risk factors for long-term prognosis of hepatocellular carcinoma patients after anatomic hepatectomy. *World J Clin cases* (2020) 8(4):713–22. doi: 10.12998/wjcc.v8.i4.713

5. Sanchez JE, Marcet JE. Colorectal natural orifice transluminal endoscopic surgery (NOTES) and transvaginal/transrectal specimen extraction. *Tech Coloproctol* (2013) 17 Suppl 1:S69–73. doi: 10.1007/s10151-012-0934-2

6. Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan ASCARE Group. The SCARE 2020 guideline: Updating consensus surgical CAse REport (SCARE) guidelines. *Int J Surg* (2020) 84:226–30. doi: 10.1016/j.ijsu.2020.10.034

7. Lancaster JM, Powell CB, Chen LM, Richardson DL. SGO clinical practice committee. society of gynecologic oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* (2015) 136(1):3–7. doi: 10.1016/j.ygyno.2014.09.009

8. Wallace H, Miller T, Angus W, Stott M. Intra-operative anaesthetic management of older patients undergoing liver surgery. *Eur J Surg Oncol* (2021) 47(3 Pt A):545–50. doi: 10.1016/j.ejso.2020.11.004

9. Heise D, Bednarsch J, Kroh A, Schipper S, Eickhoff R, Lang S, et al. Operative time, age, and serum albumin predict surgical morbidity after laparoscopic liver surgery. *Surg Innov* (2021) 28(6):714–22. doi: 10.1177/1553350621991223

10. Okimura H, Tatsumi H, Ito F, Yamashita S, Kokabu T, Kitawaki J. Endometrioid carcinoma arising from diaphragmatic endometriosis treated with laparoscopy: A case report. *J Obstet Gynaecol Res* (2018) 44(5):972–7. doi: 10.1111/jog.13595

11. Kim HJ, Choi GS, Park JS, Park SY, Jun SH. Simultaneous laparoscopic multi-organ resection combined with colorectal cancer: comparison with non-combined surgery. *World J Gastroenterol* (2012) 18(8):806–13. doi: 10.3748/wjg.v18.i8.806

12. Lee CM, Lee S, Lee D, Park S. How does combined resection affect the clinical outcomes after laparoscopic surgery for serosa-positive gastric cancer?: a retrospective cohort study to investigate the short-term outcomes of laparoscopic combined resection in patients with T4b gastric cancer. *Front Oncol* (2020) 9:1564. doi: 10.3389/fonc.2019.01564

13. Zhang L, Sun D, Zhang Y, Gao F, Guo Y. Natural orifice specimen extraction surgery in laparoscopic pancreaticoduodenectomy: A single-center case series. *Int J Surg* (2020) 82:95–9. doi: 10.1016/j.ijsu.2020.07.043

14. Guan X, Liu Z, Parvaiz A, Longo A, Saklani A, Shafik AA, et al. International consensus on natural orifice specimen extraction surgery (NOSES) for gastric cancer (2019). *Gastroenterol Rep (Oxf)* (2020) 8(1):5–10. doi: 10.1093/gastro/goz067

15. Noguera JF, Dolz C, Cuadrado A, Olea JM, Vilella A. Transvaginal liver resection (NOTES) combined with minilaparoscopy. *Rev Esp Enferm Dig* (2008) 100(7):411–5. doi: 10.4321/s1130-01082008000700006

16. Lin J, Lin S, Chen Z, Zheng B, Lin Y, Zheng Y, et al. Meta-analysis of natural orifice specimen extraction versus conventional laparoscopy for colorectal cancer. *Langenbecks Arch Surg* (2021) 406(2):283–99. doi: 10.1007/s00423-020-01934-8

17. Costantino FA, Diana M, Wall J, Leroy J, Mutter D, Marescaux J. Prospective evaluation of peritoneal fluid contamination following transabdominal vs. transanal specimen extraction in laparoscopic left-sided colorectal resections. *Surg Endosc* (2012) 26(6):1495–500. doi: 10.1007/s00464-011-2066-6

18. Song T, Kim MK, Lee YY, Choi CH, Kim TJ, Lee JW, et al. Women with double primary cancers of the colorectum and endometrium: do they have lynch syndrome? *Eur J Obstet Gynecol Reprod Biol* (2016) 199:208–12. doi: 10.1016/j.ejogrb.2015.07.018

19. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, et al. Multiple primary tumours: challenges and approaches, a review. *ESMO Open* (2017) 2(2):e000172. doi: 10.1136/esmoopen-2017-000172

20. Akabane S, Ohira M, Kobayashi T, Kuroda S, Tanimine N, Shimizu S, et al. Intrahepatic cholangiocarcinoma coinciding with a liver metastasis from a rectal carcinoma: a case report. *Surg Case Rep* (2016) 2(1):94. doi: 10.1186/s40792-016-0222-x

21. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the surveillance, epidemiology, and end results (SEER) program. *Oncologist* (2007) 12(1):20–37. doi: 10.1634/theoncologist.12-1-20

22. Okauchi S, Sasatani Y, Ohara G, Kagohashi K, Satoh H. Combined atezolizumab and chemotherapy for a patient with double primary cancers. *In Vivo* (2020) 34(1):389–92. doi: 10.21873/invivo.11785

23. Lv M, Zhang X, Shen Y, Wang F, Yang J, Wang B, et al. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. *Med (Baltimore)* (2017) 96(17):e6799. doi: 10.1097/MD.0000000000006799

24. Perutelli A, Garibaldi S, Basile S, Signori S, Boggi U, Salerno MG. Combined robotically-assisted laparoscopic left hepatectomy and total hysterectomy of enlarged uterus. *Minerva Chir* (2015) 70(5):386–8.

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 29 September 2022
DOI 10.3389/fonc.2022.994444

Check for updates

OPEN ACCESS

EDITED BY
Felix Berlth,
Johannes Gutenberg University Mainz, Germany

REVIEWED BY
Shenghui Huang,
Fujian Medical University Union Hospital, China
Michele Milella,
University of Verona, Italy

*CORRESPONDENCE
Quoc Riccardo Bao
Quocriccardo.bao@unipd.it

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 14 July 2022
ACCEPTED 13 September 2022
PUBLISHED 29 September 2022

CITATION
Bao QR, Crimì F, Valotto G, Chiminazzo V, Bergamo F, Prete AA, Galuppo S, El Khouzai B, Quaia E, Pucciarelli S and Urso EDL (2022) Obesity may not be related to pathologic response in locally advanced rectal cancer following neoadjuvant chemoradiotherapy. *Front. Oncol.* 12:994444. doi: 10.3389/fonc.2022.994444

Obesity may not be related to pathologic response in locally advanced rectal cancer following neoadjuvant chemoradiotherapy

Quoc Riccardo Bao [1*†], Filippo Crimì [2†], Giovanni Valotto [1], Valentina Chiminazzo [3], Francesca Bergamo [4], Alessandra Anna Prete [4], Sara Galuppo [5], Badr El Khouzai [5], Emilio Quaia [2], Salvatore Pucciarelli [1] and Emanuele Damiano Luca Urso [1]

[1]General Surgery 3, Department of Surgical- Oncological and Gastroenterological Sciences DiSCOG, University of Padova, Padova, Italy, [2]Institute of Radiology - Department of Medicine, University of Padova, Padova, Italy, [3]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy, [4]Unit of Medical Oncology 1, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy, [5]Radiotherapy Unit, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy

Background: The aim of this study is to evaluate the correlation between body mass index (BMI) and body fat composition (measured with radiological fat parameters (RFP)) and pathological response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer patients. The secondary aim of the study was to assess the role of BMI and RFP on major surgical complications, overall survival (OS), and disease-free survival (DFS).

Methods: All patients who underwent surgical resection following nCRT between 2005 and 2017 for mid-low rectal cancer were retrospectively collected. Visceral fat area (VFA), superficial fat area (SFA), visceral/superficial fat area ratio (V/S), perinephric fat thickness (PNF), and waist circumference (WC) were estimated by baseline CT scan. Predictors of pathologic response and postoperative complications were investigated using logistic regression analysis. The correlations between BMI and radiologic fat parameters and survival were investigated using the Kaplan–Meier method and log-rank test.

Results: Out of 144 patients included, a complete (TRG1) and major (TRG1+2) pathologic response was reported in 32 (22%) and 60 (45.5%) cases, respectively. A statistically significant correlation between BMI and all the RFP was found. At a median follow-up of 60 (35–103) months, no differences in terms of OS and DFS were found considering BMI and radiologic fat parameters. At univariable analysis, neither BMI nor radiologic fat parameters were predictors of complete or major pathologic response; nevertheless, VFA, V/S>1, and BMI were predictors of postoperative major complications.

Conclusions: We found no associations between BMI and body fat composition and pathological response to nCRT, although VFA, V/S, and BMI were predictors of major complications. BMI and RFP are not related to worse long-term OS and DFS.

KEYWORDS

radiologic fat parameters and rectal cancer outcomes rectal cancer, neoadjuvant chemoradiotherapy, pathological response, obesity, visceral fat, BMI

Introduction

Rectal cancer represents a major cause of morbidity and mortality worldwide, and the actual standard of care for locally advanced rectal cancer is total mesorectal excision (TME) following neoadjuvant chemoradiotherapy (nCRT) (1).

A high body mass index (BMI) was associated with an increased colorectal cancer risk (2, 3), and general and visceral obesity were reported as risk factors for the increased incidence of colorectal neoplasms (4). Furthermore, BMI has been linked to a worse outcome of colorectal cancer (5–8), probably due to the deregulation of IGFR-1 and other cytokines involved in metabolic syndrome, which are overexpressed in obese patients (9). IGFR-1 was correlated with a poor response after nCRT in rectal cancer (10), and visceral obesity was associated with worse outcomes in patients with stage II and III colorectal cancer in terms of surgical outcomes and recurrence (11–14).

The impact of obesity and visceral fat on response to neoadjuvant treatment was investigated in other neoplasms, such as breast cancer. Even with controversial results, the role of visceral fat in the mechanism of chemosensitivity was suggested (15, 16). In rectal cancer, obese patients were reported to have a lower rate of complete pathologic response (pCR) and a lower rate of sphincter-preserving procedures. However, no difference in terms of recurrence rate was described in obese and nonobese (6). Furthermore, Sun et al. confirmed that obese patients have a lower pCR rate, besides BMI was associated with an adverse effect on downstaging and tumor regression grade, and resulted as a strong predictor for recurrence (5).

Up to 20% of rectal cancer patients showed a pCR following nCRT, permitting also organ-sparing approaches. The identification of predictors of pathologic response, such as biological markers (i.e., carcinoembryonic antigen (CEA), microsatellite instability) (17, 18), is now essential to the best selection of patients in a rectum-sparing program. However, the impact of obesity and body fat composition on pathologic response has not been extensively assessed in the current literature.

The aim of this study is to evaluate the correlation between obesity (defined using BMI) and body fat composition (measured with radiological fat parameters (RFP)) and pathological response after nCRT for locally advanced rectal cancer patients. The secondary aim of the study was to assess the role of BMI and RFP on major surgical complications, overall survival (OS), and disease-free survival (DFS).

Methods

Patients' selection

All patients who underwent surgical resection following nCRT for locally advanced rectal cancer between 2005 and 2017 were retrospectively collected from the prospectively maintained database of the Colorectal Surgery (General Surgery 3), University Hospital of Padova. The study was notified and approved by the local Ethical Committee. Inclusion criteria were histologically confirmed mid-low rectal adenocarcinoma up to 12 cm from the anal verge surgically treated following standard nCRT. For patients treated with upfront or emergency surgery, or with recurrent disease, short-course radiotherapy was excluded. The baseline work-up included clinical history, digital rectal examination, colonoscopy, CEA level, chest/abdomen computed tomography (CT) scan, and pelvic magnetic resonance imaging (MRI).

Clinical and pathological TNM staging were reported according to the American Joint Committee on Cancer (AJCC) Eighth Edition (19). Tumor regression grade (TRG) was assessed according to Mandard's classification (20). pCR was defined as no viable tumor cell found in the surgical specimen (TRG1), while major pathologic responses as TRG1 and TRG2.

Treatment details

All the patients underwent standard nCRT with 5-FU/capecitabine and 50.4 Gy of fractioned radiotherapy. Patients who underwent short-course radiotherapy (5 × 5) were excluded to eliminate a possible confounding factor. Indication for nCRT was discussed during the multidisciplinary meeting, according to current guidelines (21, 22). Surgical resection was planned after a re-evaluation during the multidisciplinary meeting. If a complete or major clinical response was observed (23) and patients were eligible for a rectum-sparing approach in the context of other study protocols, currently running in our center (23–25), patients were treated with local excision [i.e., transanal excision, transanal endoscopic operation (TEO)]. On the contrary, if a partial/absent response was observed, or in the case of patients not eligible for rectum-sparing approach, a radical resection (i.e., TME), as low anterior resection (LAR), abdominoperineal resection (APR), or intersphinteric resection (ISR) with coloanal anastomosis, was planned. In patients treated by local excision, radicalization surgery (completion TME) was recommended when one of the high-risk features was present on the histopathological report as previously described (25). Patients treated with a rectum-sparing approach were followed up every 3 months according to study protocols (23–25). In patients treated with TME, adjuvant treatment was offered to patients with pTNM II stage with high-risk features or pTNM III stage according to national guidelines (22).

Obesity indexes and radiological fat parameters

BMI was calculated at baseline assessment as the ratio between body weight (kg)/height (m^2). For each patient, abdominal fat was calculated as previously described from the available preoperative baseline CT scan by an expert radiologist, who was blinded to clinical data (26) using reconstruction software (Fujifilm Synapse 5). The following RFP were estimated: superficial fat area (SFA), visceral fat area (VFA), total fat area (TFA), perinephric fat (PNF), waist circumference (WC), and visceral/superficial fat area ratio (V/S). The image attenuation range was set between −190 and −30 Hounsfield Unit (HU) (11). VFA and SFA were measured using a single slice at the level of the intervertebral space between L4 and L5 (Figure 1). The area of the psoas and sacrospinal muscles were excluded from the area since it may contain fatty tissue derived from age-related fatty degeneration (27). TFA was calculated by summing VFA and SFA. PNF was defined as the shortest distance (mm) between the kidney and the abdominal wall (28). WC was calculated at the level of the middle point between the last rib and the iliac crest (29). V/S was calculated as the ratio between VFA and SFA.

Statistical analysis

Continuous variables were reported as median (I–III quartiles), while qualitative variables were reported as absolute numbers and percentages. Descriptive statistical analysis was performed by dividing patients with pCR and non-pCR, and complete/major vs partial/absent pathological response (TRG3–5). Significant differences between the two groups were tested by Pearson's Chi-square for categorical variables and the Mann–Whitney *U* test for continuous variables. PNF and BMI were evaluated as both continuous and categorical variables, using as cutoff the median value (14.7 mm) for PNF and generally accepted cutoffs defined for overweight (BMI>25) and obesity (BMI>30). For V/S, two cutoffs of 0.4 and 1 were used according to the cutoffs used in the previous literature (11, 28). The correlation between BMI and RFP was evaluated with Spearman's correlation coefficient and graphically presented using a correlation plot. Predictors of pathologic response were investigated using a univariable logistic regression approach, and a multivariable model was planned to investigate the independent predictors. The Kaplan–Meier method was used to estimate the OS, DFS, local-recurrence free survival (LRFS), and distant-recurrence free survival (DRFS). The survival curves were compared using the log-rank test. Local recurrence (LR) was defined as any recurrence in the pelvis, while distant recurrence (DR) was defined as any other recurrence. The association between RFP and OS and DFS was evaluated with univariable Cox proportional hazard models. All statistical analyses were performed using R software (version 4.0.3) (30), using the RMS package (31).

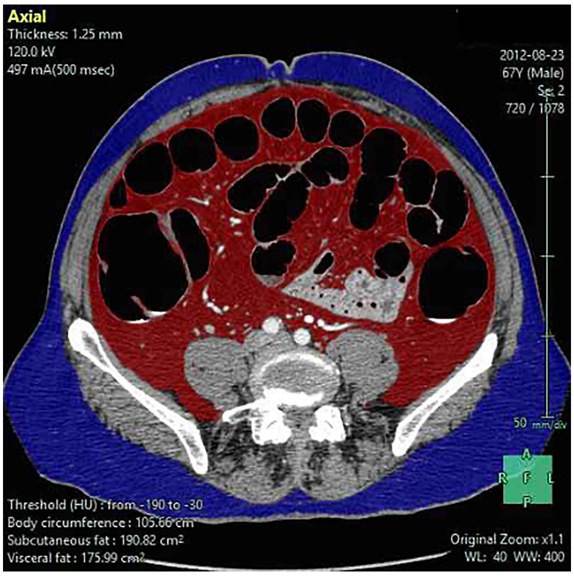


FIGURE 1
Visceral (VFA), superficial fat area (SFA), and waist circumference (WC) estimate. Superficial fat (blue), visceral fat (red), and waist circumference are estimated by using reconstruction software (Fujifilm Synapse 5).

Results

Patients, tumor, and treatment characteristics

Patients, tumor, and treatment characteristics are summarized in Table 1. Overall, 144 patients were included for analysis, 97 (67.4%) were men and 47 (32.6%) were women. The median age was 66 (58–74) years, the median distance of the tumor from the anal verge was 6.0 (4.0–9.0) cm, and the median preoperative CEA was 2.1 (1.2–4.2) ng/ml.

The median time from the completion of nCRT and surgery was 8.6 (7.0–11.4) weeks. After nCRT, 91 (63.2%) patients underwent LAR, 24 (16.7%) APR, 20 (13.9%) local excision, and nine (6.3%) ISR with coloanal anastomosis. Among TME procedures, 106 (73.6%) patients had an open traditional approach and 18 (12.5%) had a laparoscopic approach. Among the 20 patients treated with local excision, only three (15%) had negative histopathological features and required a completion TME according to the study protocol. BMI, RFP, and postoperative complications according to Clavien–Dindo are described in Supplementary Table S2. Postoperative complications occurred in 55 (38.2%) patients, and in 11 (7.6%) patients requiring re-operation (Clavien–Dindo >3a). The histopathological analysis reported a pCR in 32 (22.2%) patients, whereas a major pathologic response in 28 (21.2%), respectively.

Obesity and radiological fat parameters

Median BMI was 25.0 (22.7–27.0), median SFA, VFA, and TFA were 175.5 (124.8–227.6), 140.8 (99.9–205.1), and 318 (249–430) cm^2, respectively. Median PNF was 14.7 (7.4–22.6) mm, and median WC was 95.7 (88.4–103.8) cm. Median V/S ratio was 0.827 (0.620–1.141). The Spearman's correlation coefficient showed a statistically significant correlation between SFA ($\rho = 0.63$, $p < 0.001$), VFA ($\rho = 0.76$, $p < 0.001$), V/S ($\rho = 0.17$, $p = 0.04$), TFA ($\rho = 0.78$, $p < 0.001$) PNF ($\rho = 0.55$, $p < 0.001$), and BMI (Figure 2).

Complete and major pathologic response

The clinicopathological characteristics of patients with a pCR and a complete/major pathological response are summarized in Table 2 and Supplementary Table S1. A statistically significant difference was found between pCR and non-pCR patients regarding preoperative CEA ($p = 0.04$), distance from the anal verge ($p = 0.002$), and baseline cT stage ($p = 0.03$). No difference between the group pCR or a major pathological response regarding BMI, SFA, VFA, TFA, PNF, WC, or V/S.

Long-term outcomes and prognostic factors

Following a median follow-up of 59 (20–104) months, 20 (14.1%) patients died and 36 (25.0%) experienced recurrence. Five (3.4%) of these patients had LR, 27 (18.8%) had DR, and four (2.8%) had both LR and DR. The median OS of the whole cohort was 60.0 (34–104) months, and the median DFS was 32.0 (12.2–66.0) months. In patients with LR, the median LRFS was 18 (17–20) months, whereas the median DRFS was 15 (9–25) months. Out of the 20 patients treated with local excision, the median follow-up was 65.5 (48.8–110) months. Of these, one patient suffered LR requiring salvage TME, one patient had DR, and one patient had both LR and DR.

No differences in terms of OS, DFS, LRFS, and DRFS were found considering PNF (log-rank $p = 0.89$, $p = 0.63$, $p = 0.38$, and $p = 0.72$, respectively) (Supplementary Figure S1), BMI>25 (log-rank $p = 0.66$, $p = 0.46$, $p = 0.48$, and $p = 0.51$, respectively), BMI>30 (log-rank $p = 0.55$, 0.82, $p = 0.93$, and $p = 0.99$, respectively) (Supplementary Figure S2), V/S using a cutoff of 0.4 (log-rank $p = 0.82$, $p = 0.23$, $p = 0.85$, and $p = 0.24$, respectively), and a cutoff of 1 (log-rank $p = 0.58$, $p = 0.14$, $p = 0.30$, and $p = 0.19$, respectively) (Figure 3).

Logistic regression analysis

In a univariable logistic regression (Table 3) analysis, the baseline cT stage (OR, 4.86 (95% CI, 1.36–17.29); $p = 0.04$) and distance from the anal verge (OR, 0.22 (95% CI, 0.16–0.56); $p = 0.00$) were found to be predictors of pCR. Sex (OR, 0.42 (95% CI, 0.20–0.85); $p = 0.02$) and preoperative CEA (OR, 0.275 (95% CI, 1.07–1.98); $p = 0.01$) were linked to a significant pathological response. The general obesity index (BMI, WC) and abdominal obesity (SFA, VFA, TFA, and V/S ratio) were not predictive of pCR or major pathological response (TRG1–2).

Predictors of postoperative complications

At logistic regression analysis, VFA (OR, 2.14 (95% CI, 1.05–4.38)), V/S>1 (OR, 0.04 (95% CI, 0.04)), and BMI (OR, 1.71 (95% CI, 1.04–2.82)) were predictors of postoperative major complications.

Discussion

The present study failed to demonstrate the correlation of BMI and RFP to pathologic response after nCRT and to the long-term outcomes in locally advanced rectal cancer patients.

TABLE 1 Patients, tumor, and treatment characteristics.

	BMI < 25		BMI > 25		BMI < 30		BMI > 30		Total	
	N = 70	% or IQR	*N* = 74	% or IQR	*N* = 128	% or IQR	*N* = 16	% or IQR	*N* = 144	% or IQR
Sex										
Male	40	57	57	77	87	68	10	62	97	67.4
Female	30	43	17	23	41	32	6	38	47	32.6
Age										
Median (years)	63	55–72	68	60–77	65	56–73	70	66–76	66	58–66
BMI										
Median	22.6	21.2–23.9	26.9	26.2–29.5	24.5	22.5–26.5	32.7	31.1–36.6	25.0	22.7–27.1
PNF										
<14.7	47	71	21	30	63	52	5	31	68	49.7
≥14.7	19	29	50	70	58	48	11	69	69	50.3
V/S										
<0.4	12	16	5	4	15	10	2	12	17	12.0
≥0.4	58	84	69	96	113	90	14	88	124	88.0
<1	50	71	43	60	79	63	14	88	93	66.0
≥1	19	28	29	40	46	37	2	12	48	34.0
Clinical T stage										
cT2	14	20	6	8	19	15	1	6	20	13.9
cT3	37	53	46	62	71	55	12	75	83	57.6
cT4	19	27	22	30	38	30	3	19	41	28.5
Clinical N stage										
cN0	7	10	8	11	13	10	2	12	15	10.4
cN+	63	90	66	89	115	90	14	88	129	89.6
Surgical procedure										
Low anterior resection	44	63	47	64	82	64	9	56	91	63.2
Abdominoperineal resection	11	16	13	18	20	16	4	25	24	16.7
Local excision	10	14	10	14	17	13	3	19	20	13.9
Intersphinteric resection	5	7	4	4	9	7	0	0	9	6.3
Re-operation										
No	67	96	66	89	120	94	13	81	133	92.4
Yes	3	4	8	11	8	6	3	19	11	7.6
Grading										
G*X*	6	10	8	13	12	11	2	20	14	11.2
G1	8	13	10	16	18	16	0	0	18	14.4
G2	34	56	33	52	60	53	7	70	67	54.4
G3	13	21	12	19	24	21	1	10	25	20.0
Pathological T stage										
ypT0	18	26	14	19	27	21	5	31	32	22.2
ypTis	3	4	1	1	3	2	1	6	4	2.8
ypT1	8	11	7	9	15	12	0	0	15	10.4
ypT2	10	14	27	36	33	26	4	25	37	25.7
ypT3	26	37	23	31	43	34	6	38	49	34.0
ypT4	5	7	2	3	7	5	0	0	7	4.9
Pathological N stage										
ypN*X*	11	16	9	12	17	13	7	44	20	13.9
ypN0	40	57	44	59	77	60	7	44	84	58.3
ypN1	11	16	16	22	22	17	5	31	27	18.7
ypN2	8	11	5	7	12	9	1	6	13	9.0

(Continued)

TABLE 1 Continued

	BMI < 25		BMI > 25		BMI < 30		BMI > 30		Total	
	N = 70	% or IQR	*N* = 74	% or IQR	*N* = 128	% or IQR	*N* = 16	% or IQR	*N* = 144	% or IQR
Tumor regression grade										
TRG1	20	29	15	22	29	24	6	40	35	24.2
TRG2	12	18	16	24	26	22	2	13	28	21.2
TRG3	16	24	24	36	37	31	3	20	40	30.3
TRG4	16	24	10	15	23	19	3	20	26	19.7
TRG5	4	6	2	3	5	4	1	7	6	4.5

BMI, body mass index; PNF, perinephric fat; V/S, visceral/superficial fat area ratio; TRG, tumor regression grade.

In our findings, general obesity and visceral fat did not correlate with pathologic response, so these parameters are not to be considered contraindications for the organ-sparing approach. Moreover, obesity and visceral fat were confirmed to be predictors of postoperative major complications. Obesity is known to be associated with increased intra- and postoperative complications, and some studies reported a worse survival after surgery in rectal cancer patients after nCRT (32–34). The role of obesity and abdominal fat as prognostic factors and their impact on oncological short- and long-term outcomes were studied with controversial results. We found no significant association between obesity and radiological abdominal fat parameters considered (BMI, SFA, VFA, TFA, PNF, WC, and V/S) and the pathologic response to nCRT. In the previous literature, a few authors investigated the correlation between obesity or abdominal fat and oncological outcomes in rectal cancer after nCRT (5, 6, 28, 35), whereas others investigated the role of obesity indexes in colon and rectal cancer patients altogether (14, 33). Park et al. and Sun et al. reported on two large series of rectal cancer patients and correlated only BMI to oncological outcomes (5, 6). Park et al. reported a lower rate of pCR and a lower rate of sphincter-saving procedures in obese patients (patients with a BMI>30) (6). Similarly, Sun et al. reported that obese patients had a lower pCR rate and adverse effects on downstaging and TRG. In this study, BMI>30 was found to be a strong predictor of recurrence, with an increased 5-year LR rate in severely obese patients (5). On the other hand, in both studies, OS was not affected by BMI. However, these authors used only BMI as an obesity index, instead of a more specific radiological index such as VFA and V/S.

Han et al. (36) described the association between obesity (defined as a BMI >25) and visceral obesity (defined as a VFA ≥100) and pCR in 536 rectal cancer patients after nCRT without

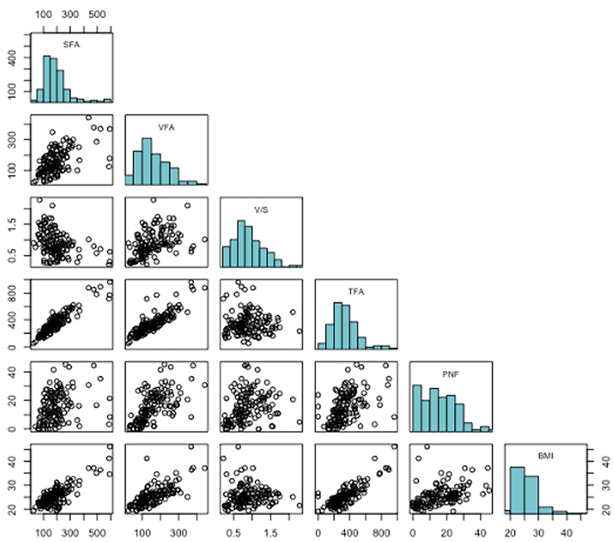


FIGURE 2
Correlation plot among BMI and radiological fat parameters.

TABLE 2 Clinicopathological characteristics of patients with a ypT0 vs. ypT1/2/3/4.

	ypT0 (*n* = 32)	ypT1/2/3/4 (*n* = 112)	Total (*n* = 144)	*p*-values
Sex				
Female (%)	13 (41)	34 (30)	47 (33)	0.275
Male (%)	19 (59)	78 (70)	97(67)	
BMI				
Median (Iqr)	24.2 (22.4–26.7)	25.1 (22.9–27.1)	25.0 (22.7–27.1)	0.514
SFA				
Median (Iqr)	195.2 (134.9–221.5)	167.5 (124.8–228.3)	175.5 (124.8–227.6)	0.518
VFA				
Median (Iqr)	132.6 (93.1–177.5)	143.1 (101.1–211.2)	140.8 (99.9–205.1)	0.324
TFA				
Median (Iqr)	336 (248–397)	313 (249–440)	318 (249–430)	0.743
PNF				
Median (Iqr)	12.3 (3.8–20.9)	15.7 (8.5–23.0)	14.7 (7.4–22.6)	0.211
WC				
Median (Iqr)	95.3 (86.4–102.0)	95.9 (88.8–104.5)	95.7 (88.4–103.8)	0.232
V/S				
Median (Iqr)	0.8 (0.5–1.0)	0.8 (0.7–1.2)	0.8 (0.6–1.1)	0.074
V/S				
<0.4	7 (22)	10 (9)	17 (12)	0.052
≥04	25 (78)	99 (91)	124 (88)	
V/S				
<1	25 (78)	68 (62)	93 (66)	0.098
≥1	7 (22)	41 (38)	48 (34)	
CEA				
Median (Iqr)	1.5 (1.1–2.8)	2.3 (1.3–4.8)	2.1 (1.2–4.2)	**0.042**
Distance a.v.				
Median (Iqr)	7.5 (6.0–9.3)	5.0 (3.8–8.0)	6.0 (4.0–9.0)	**0.002**
Distance a.v.				
<5 cm	4 (12)	41 (37)	45 (31)	**0.007**
≥5 cm	28 (88)	71 (63)	99 (69)	
cT stage				
2	6 (19)	14 (12)	20 (14)	**0.025**
3	23 (72)	60 (54)	83 (58)	
4	3 (9)	38 (34)	41 (28)	
cN stage				
0	2 (6)	13 (12)	15 (10)	0.382
1	30 (94)	99 (88)	129 (90)	
Grading				
G1	7 (29)	11 (11)	18 (14)	**< 0.001**
G2	8 (33)	60 (59)	68 (54)	
G3	2 (8)	23 (23)	25 (20)	
G*X*	7 (29)	7 (7)	14 (11)	
pN stage				
N0	18 (56)	66 (59)	84 (58)	**0.001**
N1	2 (6)	25 (22)	27 (19)	
N2	0 (0)	13 (12)	13 (9)	
N*X*	12 (38)	8 (7)	20 (14)	
PNF				

(Continued)

 10.3389/fonc.2022.994444

TABLE 2 Continued

	ypT0 (*n* = 32)	ypT1/2/3/4 (*n* = 112)	Total (*n* = 144)	*p*-values
<14.7	18 (58)	51 (48)	69 (50)	0.33
≥14.7	13 (42)	55 (52)	68 (50)	
BMI				
<25	18 (56)	55 (49)	73 (51)	0.476
≥25	14 (44)	57 (51)	71 (49)	
BMI				
<30	27 (84)	101 (90)	128 (89)	0.357
≥30	5 (16)	11 (10)	16 (11)	

BMI, body mass index; SFA, superficial fat area; VFA, visceral fat area; TFA, total fat area; V/S, visceral/superficial fat area ratio; PNF, perinephric fat; WC, waist circumference; TRG, tumor regression grade. Bold values are statistically significant values.

finding any statistical correlation between those parameters. Similarly to our study, Lee et al. investigated the role of RFP in 125 rectal cancer patients. They found that only V/S>1 was related to a higher recurrence rate, and a worse DFS and OS. However, this study did not include patients treated with nCRT (11). AV/S cutoff of 0.4 was used by Clark et al., which found that higher VFA, V/S, and BMI were related to a minor tumor downstaging, a decreased DFS, and an increased recurrence rate. Furthermore, PNF was associated with a worse OS (28). Interestingly, patients with a V/S>0.4 were statistically older and affected by other comorbidities (hypertension, hypercholesterolemia). These conditions could explain a trend toward a worse OS. Moon et al. demonstrated that a higher V/S was related to a lower DFS, without difference in terms of OS (14). Finally, Goulart et al., including colon and rectal cancer patients, reported no difference in OS and DFS by dividing VFA into quartiles (33).

In our study, BMI and VFA were confirmed to be associated with postoperative complications. It is widely assumed that surgery in obese patients is affected by increased postoperative comorbidity due to the more difficult surgery and all the comorbidity associated with metabolic syndrome. Similarly to our finding, Zhou et al. reported VFA as a strong independent predictor of postoperative complications in rectal cancer (32). However, in this study, all the

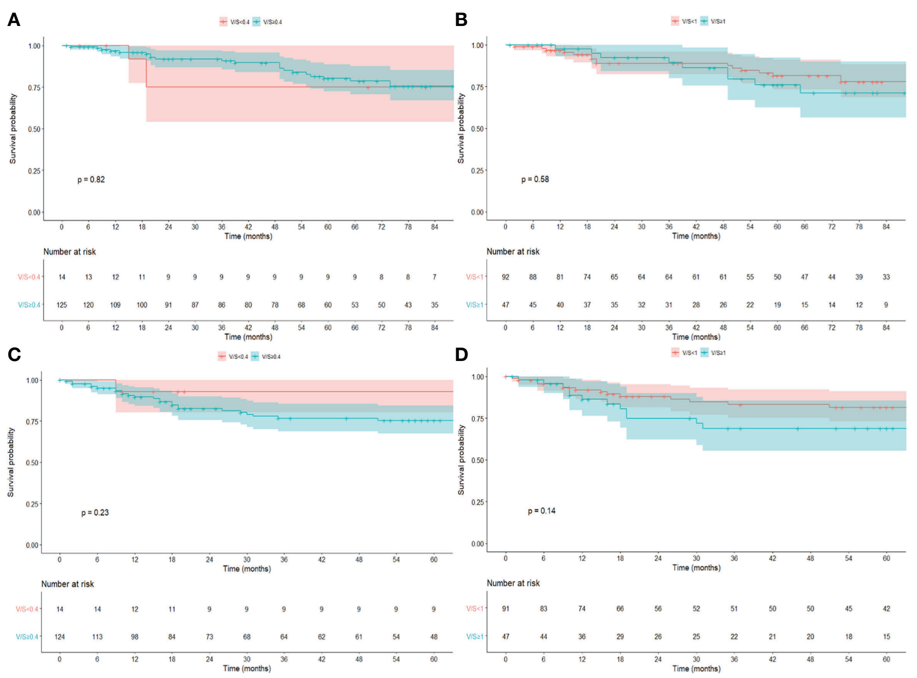


FIGURE 3
Kaplan–Meier survival estimate for OS and DFS for V/S using a cutoff of 0.4 **(A, C)** and 1.0 **(B, D)**.

TABLE 3 Logistic regression univariable analysis.

	Pathologic complete response			Pathologic major response		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex	1.566	0.70–3.54	0.28	0.418	0.20–0.85	**0.02**
Age	1.409	0.82–2.43	0.22	1.374	0.85–2.23	0.2
BMI	1.101	0.72–1.70	0.63	0.867	0.61–1.23	0.43
SFA	0.974	0.66–1.44	0.9	1.020	0.73–1.42	0.91
VFA	1.424	0.81–2.50	0.22	0.892	0.57–1.38	0.61
TFA	1.13	0.72–1.78	0.6	0.967	0.67–1.40	0.86
PNF	1.555	0.83–2.92	0.17	0.680	0.41–1.14	0.14
V/S	0.582	0.33–1.04	0.07	0.765	0.49–1.20	0.24
V/S < 0.4 vs. ≥ 0.4	0.361	0.12–1.04	0.06	1.978	0.71–5.54	0.19
V/S < 1 vs. ≥ 1	0.464	0.18–1.17	0.1	1.497	0.73–3.05	0.27
CEA < 5 vs. ≥ 5	0.497	0.16–1.55	0.23	0.275	1.07–1.98	**0.01**
Distance AV < 5 vs. ≥ 5	0.215	0.08–0.56	**< 0.01**	1.909	0.97–3.76	0.06
cT stage	4.855	1.36–17.29	**0.04**	0.717	0.33–1.55	0.56
cN stage	1.970	0.42–9.22	0.39	2.151	0.72–6.40	0.17
PNF < 14.7 vs. ≥ 14.7	1.493	0.66–3.35	0.33	0.637	0.32–1.26	0.19
BMI < 25 vs. ≥ 25	1.332	0.60–2.94	0.48	0.837	0.43–1.62	0.6
BMI < 30 vs. ≥ 30	0.588	0.19–1.84	0.36	1.370	0.48–3.88	0.55

BMI, body mass index; SFA, superficial fat area; VFA, visceral fat area; TFA, total fat area; V/S, visceral/superficial fat area ratio; PNF, perinephric fat; WC, waist circumference. Bold values are statistically significant values.

patients treated with nCRT were excluded. Heus et al. reported VFA and TFA in rectal cancer patients undergoing long-course nCRT. Using a cutoff of 100 cm^2 for VFA, an increase in operative blood loss and postoperative complications were reported (35). Even if the role of postoperative complications on the long-term oncological outcome is still debated (37), postoperative complications, as far as worse general performance status, may result in a delay in adjuvant therapy and in an increased rate of LR and a decreased survival (38, 39).

The available literature on rectal cancer patients, obesity parameters, pCR, and other oncological outcomes has given conflicting results, mainly because in different studies, there are different inclusion criteria, methods, and main objectives and endpoints. With these limitations, there is no agreement on the role of obesity and its related radiological parameters on oncological outcomes in locally advanced rectal cancer patients treated with nCRT and surgery. Conflicting data exist on the role of obesity index on pathological response to nCRT, and only BMI was considered by Sun et al. and Park et al. (the studies with the largest number of patients included), while RFPs were not investigated (5, 6). Unlike oncological outcomes, we can find agreement in the literature on finding an association between most obesity index and perioperative complications. Based on the data available in the present study, obesity cannot basically influence oncological decision-making, but it is a predictor of a higher rate of surgical complications.

Our study does have some limitations. First is the small number of enrolled patients when compared with a few similar previous publications, even if only the study of Clark et al. has the same inclusion criteria and the same methods we used (28). Clark et al. analyzed the same obesity parameters we considered in a group of 99 rectal cancer patients treated with nCRT, finding that elevated V/S or PNF was associated with shorter DFS and OS. The relationships between BMI, RFPs, pathologic response, and postoperative complications were not investigated. From this point of view, our study investigated the largest group of locally advanced rectal cancer patients, all surgically treated after a neoadjuvant approach, considering BMI and all the most known RFPs, in association with pCR, OS, DFS, and perioperative complications. Despite these considerations, the relatively small number of patients enrolled could cover the predictive prognostic potential of some of the parameters studied in many of the analyses presented. For this reason, also, we did not use a multivariable model to investigate the independent predictors of complete/major pathologic response since none of the parameters considered resulted as a predictor of pathologic response.

Second, its retrospective design, even if the clinical data were prospectively maintained in our database, whereas RFP was retrospectively collected from CT scans, and the number of enrolled patients is smaller than in other studies. Third, we arbitrarily used different cutoffs for the RFP considered since there is no strong evidence, nor agreement, in the current literature about this topic. Further studies are needed to establish the proper cutoff of these indexes. Furthermore, we considered altogether different surgical procedures such as TME and local excision. Considering that the primary aim of the study is to assess a correlation between body fat and tumor regression, we think that patients enrolled in an organ-preservation prospective clinical study

(ReSARCH trial) (23) with an accurate and standardized histopathological analysis and a long-term follow-up are eligible for the analysis, even if no pathological data are available on their mesorectal status. Last, we are analyzing the effect of nCRT on an Italian cohort, where the median BMI ranges between 24 and 26, and the rate of obesity and overweight is 10% and 35%, respectively (40). To note, this is the first study to analyzed the relationship between obesity and oncological outcomes in a group of Italian rectal cancer patients, whereas most of the cited studies are from the USA or China, where the estimated rate of obesity is greater than 36% and 16%, respectively (41, 42).

Conclusions

We found no associations between BMI and RFP and pathological response to nCRT, although VFA, V/S, and BMI were predictors of major surgical complications. BMI and RFP are not related to worse long-term OS and DFS.

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 Comitato Etico per la Sperimentazione Clinica della Provincia di Padova. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study concepts: QB, FC, EQ, SP, EU. Study design: QB, FC, EU. Data acquisition: QB, FC, GV, FB, AP, SG, BK. Data analysis and interpretation: QB, FC, GV, FB, AP, SG, BK. Statistical analysis: FC, VC. Manuscript preparation: QB, FC, GV. Manuscript editing: VC, FB, AP, SG, BK. Manuscript review: QB, EQ, SP, EU. All the authors revised and approved the final version of the manuscript.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.994444/full#supplementary-material

References

1. Ma B, Gao P, Wang H, Xu Q, Song Y, Huang X, et al. What has preoperative radio(chemo)therapy brought to localized rectal cancer patients in terms of perioperative and long-term outcomes over the past decades? A systematic review and meta-analysis based on 41,121 patients. *Int J Cancer* (2017) 141 (5):1052–65. doi: 10.1002/ijc.30805

2. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut* (2013) 62(6):933–47. doi: 10.1136/gutjnl-2013-304701

3. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H, et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: Findings from cancer and leukemia group b 89803. *J Clin Oncol* (2008) 26(25):4109–15. doi: 10.1200/JCO.2007.15.6687

4. Murphy N, Carreras-Torres R, Song M, Chan AT, Martin RM, Papadimitriou N, et al. Circulating levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 associate with risk of colorectal cancer based on serologic and mendelian randomization analyses. *Gastroenterology* (2020) 158(5):1300–12: e20. doi: 10.1053/j.gastro.2019.12.020

5. Sun Y, Xu Z, Lin H, Lu X, Huang Y, Huang S, et al. Impact of body mass index on treatment outcome of neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Eur J Surg Oncol* (2017) 43(10):1828–34. doi: 10.1016/j.ejso.2017.07.022

6. Park IJ, You YN, Skibber JM, Rodriguez-Bigas MA, Das P, Eng C, et al. Oncologic and functional hazards of obesity among patients with locally advanced rectal cancer following neoadjuvant chemoradiation therapy. *Am J Clin Oncol* (2017) 40(3):277–82. doi: 10.1097/COC.0000000000000150

7. Choi Y, Lee YH, Park SK, Cho H, Ahn KJ. Association between obesity and local control of advanced rectal cancer after combined surgery and radiotherapy. *Radiat Oncol J* (2016) 34(2):113–20. doi: 10.3857/roj.2016.01725

8. Scarpa M, Ruffolo C, Erroi F, Fiorot A, Basato S, Pozza A, et al. Obesity is a risk factor for multifocal disease and recurrence after colorectal cancer surgery: A case-control study. *Anticancer Res* (2014) 34(10):5735–41.

9. Berryman DE, Glad CA, List EO, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. *Nat Rev Endocrinol* (2013) 9(6):346–56. doi: 10.1038/nrendo.2013.64

10. Wu XY, Wu ZF, Cao QH, Chen C, Chen ZW, Xu Z, et al. Insulin-like growth factor receptor-1 overexpression is associated with poor response of rectal cancers to radiotherapy. *World J Gastroenterol* (2014) 20(43):16268–74. doi: 10.3748/wjg.v20.i43.16268

11. Lee KH, Kang BK, Ahn BK. Higher visceral fat area/subcutaneous fat area ratio measured by computed tomography is associated with recurrence and poor survival in patients with mid and low rectal cancers. *Int J Colorectal Dis* (2018) 33 (9):1303–7. doi: 10.1007/s00384-018-3065-z

12. Choi MH, Oh SN, Lee IK, Oh ST, Won DD. Sarcopenia is negatively associated with long-term outcomes in locally advanced rectal cancer. *J Cachexia Sarcopenia Muscle* (2018) 9(1):53–9. doi: 10.1002/jcsm.12234

13. Rickles AS, Iannuzzi JC, Mironov O, Deeb AP, Sharma A, Fleming FJ, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? *J Gastrointest Surg* (2013) 17(1):133–43. doi: 10.1007/s11605-012-2045-9

14. Moon HG, Ju YT, Jeong CY, Jung EJ, Lee YJ, Hong SC, et al. Visceral obesity may affect oncologic outcome in patients with colorectal cancer. *Ann Surg Oncol* (2008) 15(7):1918–22. doi: 10.1245/s10434-008-9891-4

15. Omarini C, Palumbo P, Pecchi A, Draisci S, Balduzzi S, Nasso C, et al. Predictive role of body composition parameters in operable breast cancer patients treated with neoadjuvant chemotherapy. *Cancer Manag Res* (2019) 11:9563–9. doi: 10.2147/CMAR.S216034

16. Farr A, Stolz M, Baumann L, Bago-Horvath Z, Oppolzer E, Pfeiler G, et al. The effect of obesity on pathological complete response and survival in breast cancer patients receiving uncapped doses of neoadjuvant anthracycline-taxane-based chemotherapy. *Breast* (2017) 33:153–8. doi: 10.1016/j.breast.2017.04.001

17. Wallin U, Rothenberger D, Lowry A, Luepker R, Mellgren A. CEA - a predictor for pathologic complete response after neoadjuvant therapy for rectal cancer. *Dis Colon Rectum* (2013) 56(7):859–68. doi: 10.1097/DCR.0b013e31828e5a72

18. Hasan S, Renz P, Wegner RE, Finley G, Raj M, Monga D, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (PCR) in locally advanced rectal cancer: A national cancer database (NCDB) analysis. *Ann Surg* (2020) 271(4):716–23. doi: 10.1097/SLA.0000000000003051

19. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: A Cancer J Clin* (2017) 67(2):93–9. doi: 10.3322/caac.21388

20. Mandard A-M, Dalibard F, Mandard J-C, Marnay J, Henry-Amar M, Petiot J-F, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. *Clinicopathol Correlations Cancer* (1994) 73(11):2680–6. doi: 10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c

21. *National comprehensive cancer network. rectal cancer (Version 1.2022)* (2022). Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.

22. AIOM. *Linee guida NEOPLASIE DEL RETTO e ANO* (2021). Available at: https://snlg.iss.it/wp-content/uploads/2021/11/LG-279-Retto-e-Ano_agg2021.pdf.

23. Barina A, De Paoli A, Delrio P, Guerrieri M, Muratore A, Bianco F, et al. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. *Tech Coloproctol* (2017) 21(8):633–40. doi: 10.1007/s10151-017-1665-1

24. Valentini V, Gambacorta MA, Cellini F, Aristei C, Coco C, Barbaro B, et al. The INTERACT trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)-cT3 rectal cancer. *Radiother Oncol* (2019) 134:110–8. doi: 10.1016/j.radonc.2018.11.023

25. D'Alimonte L, Bao QR, Spolverato G, Capelli G, Del Bianco P, Albertoni L, et al. Long-term outcomes of local excision following neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Ann Surg Oncol* (2021) 28 (5):2801–8. doi: 10.1245/s10434-020-09243-6

26. Gradmark AM, Rydh A, Renström F, De Lucia-Rolfe E, Sleigh A, Nordström P, et al. Computed tomography-based validation of abdominal adiposity measurements from ultrasonography, dual-energy X-ray absorptiometry and anthropometry. *Br J Nutr* (2010) 104(4):582–8. doi: 10.1017/S0007114510000796

27. Yang KL, Yang SH, Liang WY, Kuo YJ, Lin JK, Lin TC, et al. Carcinoembryonic antigen (CEA) level, CEA ratio, and treatment outcome of rectal cancer patients receiving pre-operative chemoradiation and surgery. *Radiat Oncol* (2013) 8:43. doi: 10.1186/1748-717X-8-43

28. Clark W, Siegel EM, Chen YA, Zhao X, Parsons CM, Hernandez JM, et al. Quantitative measures of visceral adiposity and body mass index in predicting rectal cancer outcomes after neoadjuvant chemoradiation. *J Am Coll Surg* (2013) 216(6):1070–81. doi: 10.1016/j.jamcollsurg.2013.01.007

29. Ma WY, Yang CY, Shih SR, Hsieh HJ, Hung CS, Chiu FC, et al. Measurement of waist circumference: midabdominal or iliac crest? *Diabetes Care* (2013) 36(6):1660–6. doi: 10.2337/dc12-1452

30. R Development Core Team. *R: A language and environment for statistical computing.* Vienna, Austria (2022). Available at: http://www.r-project.org/index.html

31. Harrell FEJr. *Rms: Regression modeling strategies* (2020). Available at: https://CRAN.R-project.org/package=rms.

32. Zhou CJ, Cheng YF, Xie LZ, Hu WL, Chen B, Xu L, et al. Metabolic syndrome, as defined based on parameters including visceral fat area, predicts complications after surgery for rectal cancer. *Obes Surg* (2020) 30(1):319–26. doi: 10.1007/s11695-019-04163-1

33. Goulart A, Malheiro N, Rios H, Sousa N, Leão P. Influence of visceral fat in the outcomes of colorectal cancer. *Dig Surg* (2019) 36(1):33–40. doi: 10.1159/000486143

34. Balentine CJ, Wilks J, Robinson C, Marshall C, Anaya D, Albo D, et al. Obesity increases wound complications in rectal cancer surgery. *J Surg Res* (2010) 163(1):35–9. doi: 10.1016/j.jss.2010.03.012

35. Heus C, Cakir H, Lak A, Doodeman HJ, Houdijk AP. Visceral obesity, muscle mass and outcome in rectal cancer surgery after neo-adjuvant chemo-radiation. *Int J Surg* (2016) 29:159–64. doi: 10.1016/j.ijsu.2016.03.066

36. Han JS, Ryu H, Park IJ, Kim KW, Shin Y, Kim SO, et al. Association of body composition with long-term survival in non-metastatic rectal cancer patients. *Cancer Res Treat* (2020) 52(2):563–72. doi: 10.4143/crt.2019.249

37. Bao QR, Pellino G, Spolverato G, Restivo A, Deidda S, Capelli G, et al. The impact of anastomotic leak on long-term oncological outcomes after low anterior resection for mid-low rectal cancer: extended follow-up of a randomised controlled trial. *Int J Colorectal Dis* (2022) 37(7):1689–98. doi: 10.1007/s00384-022-04204-9

38. Koedam TWA, Bootsma BT, Deijen CL, van de Brug T, Kazemier G, Cuesta MA, et al. Oncological outcomes after anastomotic leakage after surgery for colon or rectal cancer: Increased risk of local recurrence. *Ann Surg* (2022) 275(2):e420–7. doi: 10.1097/SLA.0000000000003889

39. Kulu Y, Tarantio I, Warschkow R, Kny S, Schneider M, Schmied BM, et al. Anastomotic leakage is associated with impaired overall and disease-free survival after curative rectal cancer resection: a propensity score analysis. *Ann Surg Oncol* (2015) 22(6):2059–67. doi: 10.1245/s10434-014-4187-3

40. Istituto Superiore di Sanità. *Dati epidemiologici* . Available at: https://www.epicentro.iss.it/obesita/epidemiologia-italia.

41. *Obesity rate by state* (2021). Available at: https://worldpopulationreview.com/state-rankings/obesity-rate-by-state.

42. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol* (2021) 9(6):373–92. doi: 10.1016/S2213-8587(21)00045-0

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 21 October 2022
DOI 10.3389/fonc.2022.959650

Check for updates

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Lino Polese,
University of Padua, Italy
Luca Saadeh,
University Hospital of Padua, Italy

*CORRESPONDENCE
Corrado Pedrazzani
corrado.pedrazzani@univr.it

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

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 01 June 2022
ACCEPTED 03 October 2022
PUBLISHED 21 October 2022

CITATION
Turri G, Caliskan G, Conti C, Martinelli L, De Giulio E, Ruzzenente A, Guglielmi A, Verlato G and Pedrazzani C (2022) Impact of age and comorbidities on short- and long-term outcomes of patients undergoing surgery for colorectal cancer. *Front. Oncol.* 12:959650. doi: 10.3389/fonc.2022.959650

Impact of age and comorbidities on short- and long-term outcomes of patients undergoing surgery for colorectal cancer

Giulia Turri[1†], Gulser Caliskan[2†], Cristian Conti[1], Luigi Martinelli[2], Ernesto De Giulio[1], Andrea Ruzzenente[1], Alfredo Guglielmi[1], Giuseppe Verlato[2] and Corrado Pedrazzani[1*]

[1]Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy, [2]Department of Diagnostic and Public Health, University of Verona, Verona, Italy

Background: As the world population is progressively ageing, more and more elderly patients will require cancer surgery. Although curative surgery is the treatment of choice for resectable colorectal cancer (CRC), it is still debated whether elderly frail patients should undergo major cancer surgery due to the increased risk of postoperative and long-term mortality. The aim of this retrospective study was to evaluate the impact of age and comorbidities on postoperative mortality/morbidity and long-term outcomes, looking for potential age-related survival differences.

Methods: A total of 1,482 patients operated for CRC at our institution between January 2005 and October 2020 were analysed. The independent effect of age and comorbidities on postoperative complications was assessed by a logistic model, while the effect on overall survival (OS) and cancer-related survival (CRS) was estimated by a Cox regression model.

Results: The median age in the cohort was 67.8 years. Postoperative mortality was very low in the whole cohort (0.8%) and contained even in older age groups (3.2% in patients aged 80–84 years, 4% in the 85–90-year age group). The cumulative incidence of postoperative complications was doubled in patients with comorbidities (32.8% vs. 15.1%, $p = 0.002$). With regard to OS, as expected, it exponentially decreased with advancing age. Conversely, differences in CRS were less pronounced between age groups and absent in patients with stage 0–I CRC. Analysis of all causes and cancer-related mortality revealed a peak within 2 years from surgery, suggesting a prolonged impact of surgery. In patients aged 75 years and above, all-cause mortality showed a steep increase 1 year after surgery, while cancer-related mortality plateaued at about 4 years after surgery. On multivariable analysis, OS, but not CRS, was significantly influenced by age.

Conclusions: Although acceptable results of surgery in elderly patients, OS is strongly dependent on age: older people die more from competing causes than cancer-related treatments compared to younger age classes. The preoperative identification of risk factors for low OS may help the selection of those elderly patients who would benefit from curative CRC surgery.

KEYWORDS

elderly patients, colorectal cancer surgery, survival, comorbidities, mortality

Introduction

Colorectal cancer (CRC) is one of the most common tumours worldwide, and its incidence increases with age, with a median age at diagnosis of 67 years (1). As the world population is progressively ageing, more and more elderly patients with CRC will require surgical treatment. Curative surgery is the treatment of choice for resectable CRC, and some current literature suggests that elderly patients have the same oncological benefit as younger patients (2, 3). However, it is still debated whether an invasive treatment should be performed in elderly patients (4, 5), due to the increased risk of postoperative complications, mortality, and difficulty to regain independence (6, 7). Furthermore, the definition of elderly is controversial. Even though the conventional definition of elderly refers to a person aged 65 years or more, frequently chronological age does not correspond to the biological one (8, 9). In fact, older age does not always correspond to frailty and more comorbidities. Therefore, to assess surgical risk in elderly patients, postoperative outcomes according to age classes were extensively investigated. Previous studies evaluated age-related morbidity and mortality in a short-term period, focusing on postoperative outcomes (10, 11). Despite the demonstration of acceptable short-term results after colorectal cancer surgery in older patients, the elderly population represents a heterogeneous cohort and may suffer from late complications as difficulty to thrive beyond 30 days after surgery (12, 13). Furthermore, 30-day mortality may underestimate surgical risk even in younger patients, as a not negligible proportion of them die beyond this time frame (14, 15). Interestingly, Dekker et al. showed a significant excess mortality in the first year after colorectal surgery in elderly patients, while those who survived thereafter showed the same cancer-related survival as younger patients (16). This excess mortality involved especially patients with comorbidities, higher stages of disease, emergency surgery, and postoperative complications, reaching 15%–30% in high-risk patients (17). Currently, the treatment of elderly patients with CRC represents a modern challenge of personalised medicine, balancing undertreatment based on the sole chronological age and overtreatment of frail patients (18–20).

The aim of this retrospective study was to evaluate the impact of age and comorbidities on postoperative mortality/morbidity and long-term outcomes on a large cohort of surgically treated CRC patients, and to evaluate the opportunity to submit elderly and frail patients to surgery.

Material and methods

Study population

The initial cohort of patients included 1,645 patients who had surgery for CRC at the Division of General and Hepatobiliary Surgery, University of Verona Hospital Trust, between January 2005 and October 2020. All elective and urgent surgeries and stage 0–IV, potentially curative (R0–1), and palliative (R2) procedures were included. Patients below the age of 30 and above the age of 90 were excluded, as the numbers in those age categories were very exiguous. Patients with missing follow-up data were also excluded. After application of inclusion criteria, 1,482 patients were analysed (Figure 1). Patients were classified in age classes as younger patients (<65 years) and elderly patients (65–69, 70–74, 75–79, 80–84, 85–89 years). Demographic, clinical, pathological, and pre- and postoperative data were retrieved from a retrospective database. All patients were staged with preoperative colonoscopy, chest–abdomen–pelvis computed tomography (CT), and carcinoembryonic antigen (CEA) measurement. The main goal of surgery was the complete excision of the cancer to obtain an R0 resection. The extent of the resection was planned according to cancer location, disease stage, and patient's general conditions. Anatomical resections with ligation of vessels at their origin were the procedures of choice in order to achieve an adequate lymphadenectomy. The surgical approach included open and laparoscopic resections according to the surgeons' preference, with laparoscopy becoming the preferred approach after 2014. Comorbidity status was assessed using the Charlson

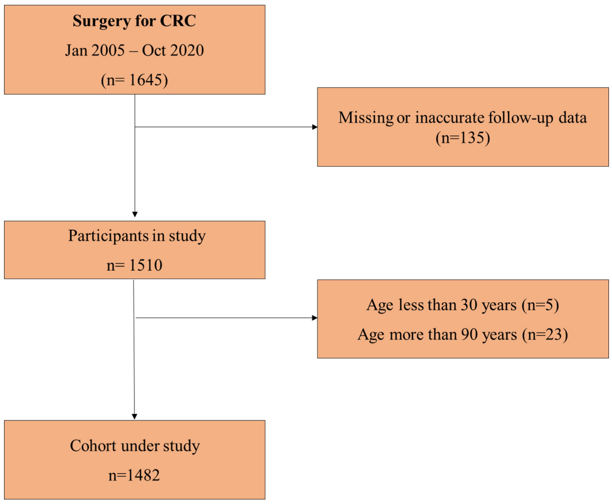


FIGURE 1
Flowchart depicting the selection process of patients under study.

Age Comorbidity Index (CACI) (21). Tumours were staged according to the 8th Edition of the AJCC Cancer Staging Manual (22). Patients with locally advanced rectal cancer underwent long-course chemoradiotherapy or exclusive radiotherapy according to performance status and comorbidities. Preoperative chemotherapy was administered to patients with stage IV CRC depending on multidisciplinary assessment. Adjuvant chemotherapy was considered for patients with stage III/IV disease or stage II with risk factors after multidisciplinary discussion. Survival and follow-up data were obtained by revising outpatient clinical records for patients undergoing regular clinical follow-up or receiving oncological treatment at our centre. In the case of patients attending follow-up visits at other institutions, a member of our staff conducted a telephone follow-up at least once a year by directly contacting the patient or the relatives. Overall survival (OS) was defined as the length of time between primary surgery and time of death from any cause, whereas cancer-related survival (CRS) considered death from cancer or cancer-related treatment (i.e., postoperative mortality or toxicity/adverse events after chemotherapy) as the end point.

Statistical analyses

The primary outcome variables were postoperative mortality and long-term OS and CRS. The main predictors considered in the present study were age, coded as <65, 65–69, 70–74, 75–79, 80–84, and 85–89 years, stage (stage 0–I, stage II, stage III, stage IV), gender (male, female), comorbidities (yes, no), tumour location (right colon, left colon, rectum), type of surgery (urgent, elective), neoadjuvant therapy (yes versus no), adjuvant therapy (yes versus no), radicality of surgery (R0–1 versus R2), postoperative complications (yes, no), and number of analysed lymph nodes (<12, ≥12). Significance of the association between age class and postoperative mortality was evaluated by Fisher's exact test, and results are presented as n (%). Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to evaluate the significance of differences among curves. To plot the estimated hazard function, a kernel smoother was used with a bandwidth of 0.2 years. The independent effect of age class on overall or cancer-related survival was evaluated by a Cox regression model, adjusting for gender, stage, comorbidity, and neoadjuvant and adjuvant chemotherapy. To test whether the prognostic significance of the main risk factors changed over time, the proportional hazards assumption of the Cox model was tested on the basis of Schoenfeld residuals. Life expectancy was compared between the CRC cohort and the general population from Verona. The comparison was restricted to patients undergoing R0–R1 surgery and to the age class 80–84 years, where median and mean survival could be computed for the CRC cohort. Life expectancy of the CRC cohort was extrapolated, as some patients were still alive at the end of follow-up, while life expectancy in the Verona general population was yielded by the Italian National Institute of Statistics (https://demo.istat.it/tvm2016). *p*-values below 0.05 were considered statistically significant. The statistical analysis was performed using STATA software, release 17.0 (StataCorp, College Station, TX, USA).

Results

Cohort under study

Table 1 reports the main demographic and clinical characteristics of the included patients. The median age in the cohort was 67.8 years (IQR 58.8–76.9 years). The proportion of female patients increased significantly with increasing age ($p < 0.001$), as well as the median CACI ($p < 0.001$) and the presence of comorbidities (46.7% in patients aged below 65 years versus 77.6% in patients 85–89 years, $p > 0.001$). The percentage of patients undergoing surgery for rectal cancer decreased with increasing age (32.3% in patients aged <65 versus 10.5% in patients aged 85–89, $p < 0.001$), while the predominant site in the elderly was the right colon. Neoadjuvant treatment was more frequently used in younger patients (23.8% in patients aged <65 versus 7.9% in patients ages 80–84, $p < 0.001$). Interestingly, neoadjuvant treatment in patients aged <75 included both preoperative chemotherapy for metastatic CRC and neoadjuvant chemoradiotherapy for rectal cancer. On the contrary, most of patients aged >75 received neoadjuvant chemoradiotherapy for rectal cancer ($p = 0.009$).

Most patients underwent elective surgery, but the proportion of urgent surgeries increased with increasing age ($p < 0.001$). Thirty-day postoperative mortality in the whole cohort was low and within acceptable ranges in all age groups (0.8%). Patients aged 80 years and above presented the highest postoperative mortality (3.2% in patients aged 80–84 years and 4% in patients aged 85–89 years, $p < 0.001$). Only patients with at least one comorbidity died in the postoperative period (12/928 = 1.3%). Finally, postoperative complications occurred more often in elderly patients (22.6% in patients aged below 65 versus 31.6%

TABLE 1 Characteristics of the cohort under study by age classes.

	Age classes						P value
	<65 years (n = 615)	**65–69 years (n = 242)**	**70–74 years (n = 200)**	**75–79 years (n = 193)**	**80–84 years (n = 156)**	**85–89 years (n = 76)**	
Gender, female	279 (45.4%)	87 (36.0%)	69 (34.5%)	87 (45.1%)	75 (48.1%)	47 (61.8%)	**< 0.001**
Comorbidities, yes	287 (46.7%)	158 (65.3%)	140 (7.0%)	146 (75.6%)	138 (88.5%)	59 (77.6%)	**< 0.001**
CACI, median (IQR)	4 (3-5)	5 (4-6)	6 (5-7)	6 (5-7)	7 (6-8)	7 (6-8)	**< 0.001**
CACI ≥5	160 (25.8%)	109 (45%)	172 (86%)	166 (86.1%)	152 (96.8%)	65 (85.5%)	**< 0.001**
BMI, median (IQR)	24.8 (22.5-27.9)	25.5 (23.4-27.5)	25.6 (23.8-27.9)	24.9 (22.5-28.0)	26.1 (23.3-28.3)	24.2 (21.6-27.5)	0. 23
Elective surgery	593 (96.4%)	231 (95.5%)	194 (97.0%)	179 (92.8%)	143 (91.7%)	65 (85.5%)	**< 0.001**
Laparoscopic surgery	206 (33.5%)	83 (34.3%)	51 (25.5%)	47 (24.4%)	34 (21.8%)	22 (29.0%)	**0.008**
Postoperative mortality	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (1.0%)	5 (3.2%)	3 (4.0%)	**< 0.001**
Postoperative complications	139 (22.6%)	61 (25.2%)	53 (26.5%)	60 (31.1%)	54 (34.6%)	24 (31.6%)	**0.008**
Neoadjuvant therapy, yes*	129 (23.8%)	34 (16.0%)	18 (10.0%)	19 (11.2%)	11 (7.9%)	0 (0.0%)	**< 0.001**
Neoadjuvant type							
CHT	53 (41.1%)	15 (44.1%)	9 (50.0%)	5 (26.3%)	1 (9.1%)	-	**0.009**
CRT	73 (56.6%)	17 (50.0%)	9 (50.0%)	13 (68.4%)	6 (54.5%)	-	
RT	3 (2.3%)	2 (5.9%)	0 (0.0%)	1 (5.3%)	4 (36.4%)	-	
Tumour location							
Left colon	256 (41.6%)	95 (39.2%)	91 (45.5%)	68 (35.2%)	54 (34.6%)	27 (35.5%)	**< 0.001**
Right colon	165 (26.8%)	84 (34.7%)	66 (33.0%)	74 (38.3%)	64 (41.0%)	41 (53.9%)	
Rectum	199 (32.3%)	63 (26.0%)	43 (21.5%)	51 (26.4%)	39 (25.0%)	8 (10.5%)	
Stage							
0–I	197 (31.8%)	84(34.7%)	50 (25%)	50 (26%)	34 (21.8%)	11 (14.5%)	**< 0.001**
II	127 (20.5%)	62 (25.6%)	64 (32%)	67 (35%)	55 (35.2%)	29 (38.2%)	
III	151 (24.4%)	50 (20.7%)	55 (27.5%)	43 (22.4%)	42 (27%)	21 (27.6%)	
IV	144 (23.3%)	46 (19%)	31 (15.5%)	32 (16.6%)	25 (16%)	13 (17.1%)	
Potentially curative (R0–1)	539 (87.6%)	219 (90.5%)	176 (88%)	170 (88.1%)	140 (89.7%)	63 (82.9%)	0.540
Adjuvant therapy, yes°	93 (20.2%)	27 (14.5%)	21 (13.5%)	9 (6.0%)	6 (5.1%)	2 (3.8%)	**< 0.001**
Number of retrieved lymph-nodes ≥12	526 (87.1%)	204 (85.7%)	158 (81.0%)	148 (79.1%)	125 (81.2%)	54 (77.1%)	**0.027**

Data are expressed as number of patients (%) or median (IQR).
CACI (Charlson-Age Comorbidity Index); BMI (body max index).
*Information available for 1,317/1,482 patients.
°Information available for 1,121/1,482 patients.
p values – 0.05 were highlighted in bold.

in patients aged 85–89 years, $p = 0.008$), and its occurrence was strictly associated with the presence of comorbidities (32.8% in patients with comorbidities versus 15.1% in patients without comorbidities, $p = 0.002$). Similarly to neoadjuvant treatment, adjuvant therapy was most frequently adopted in younger patients (20.2% in patients aged <65 versus 3.8% in patients aged 85–89, $p < 0.001$).

There was a non-linear relationship between stage and age. Stage 0–I and IV were more frequent in the youngest age group, where older patients presented a higher proportion of stage II and III CRC ($p < 0.001$). The radicality of surgery did not differ significantly between age groups as demonstrated by the similar proportions of potentially curative resections (R0–1).

Long-term outcomes

As expected, OS markedly differed among the six age classes (Supplementary Figure 1, $p < 0.001$) and decreased progressively with increasing age. The difference was blunted when considering only deaths related to cancer or cancer treatment (Supplementary Figure 2, $p < 0.001$). Supplementary Tables 1–3 report OS and CRS stratified by age classes and gender, stages, and comorbidity status. OS was significantly poorer in older patients regardless of gender, stage, and comorbidities. With regard to CRS, male patients showed similar survival rates in all age classes ($p = 0.198$). When stratifying for stage, CRS did not differ significantly between the six age groups in patients with stage 0–I CRC ($p = 0.072$), but it was affected by age in the elderly groups. Finally, the presence of comorbidities influenced both OS ($p < 0.001$) and CRS ($p = 0.012$).

Age classes were then grouped into three categories to obtain adequate precision in estimating the hazard of mortality during follow-up: <65 years, 65–75, and 76–89 years. The smoothed hazard of mortality from CRC and from all causes is presented in the upper panel of Figure 2, while the lower panel shows survival curves estimated with the Kaplan–Meier method. Interestingly, the smoothed hazard of mortality from all causes was significantly higher in the 76–89 age class, while the other two age groups presented a similar hazard. The trend however was similar in all groups, with a peak of the hazard of all-cause mortality approximately 2 years after surgery and cancer-related mortality within the first 18 months. Cumulative cancer-related mortality and all-cause mortality were plotted separately for the three age groups using the Kaplan–Meier method (Figure 3). In younger patients, curves of cumulative all-cause mortality and cancer-related mortality over time were rather close throughout the follow-up time. On the contrary, the curves tended to separate already 1 year after surgery in CRC patients aged over 75 years, due to a larger mortality from causes other than cancer.

Multivariable analysis

Multivariable analysis was conducted to assess the impact of age and comorbidities on OS and CRS (Table 2). OS was significantly influenced by age, comorbidities, stage, radicality of surgery, occurrence of postoperative complications, number of retrieved lymph nodes <12, and neoadjuvant treatment. On the contrary, age and comorbidities did not prove to be independent prognostic factors for CRS, which was only dependant on stage and neoadjuvant therapy.

Comparison between the CRC cohort and the general population

Life expectancy was compared between the CRC cohort, undergoing R0–R1 surgery, and the general population from Verona. The comparison was restricted to the age class 80–84 years, where the median and mean survival could be computed for the CRC cohort. Patients in stage 0–I had the same life expectancy of the Verona general population: life expectancy was 8.74 and 9.67 years, respectively, in male and female CRC patients, compared to 8.27 and 10.58 years in men and women from the Verona general population. Life expectancy was markedly reduced in stage III patients (5.3 years in men and 3.7 years in women) and furthermore in stage IV patients (2.3 and 2.2 years, respectively). Life expectancy in stage II patients was affected by gender, as it was similar to that of the general population in men (7.4 years) and substantially reduced in women (5.7 years).

Discussion

The primary aim of the present study was to determine the long-term outcomes of elderly patients undergoing CRC surgery and to evaluate whether all age groups benefit from surgery. The treatment of CRC in elderly patients represents a contemporary dilemma as the world population is progressively ageing (23), and CRC exhibits a peak incidence around seventy years in both sexes (24).

Despite poorer OS in elderly patients, postoperative mortality was very low in the whole cohort (0.8%), and within acceptable ranges even in octogenarian patients (3%–4%). These data are in line with the current literature (25–27) and suggest that cancer surgery can be feasible with contained postoperative mortality even in older patients. It should be noted that postoperative mortality occurred only in patients aged 65 and above and with concurrent comorbidities, while younger and fit patients did not suffer any postoperative death. Prehabilitation

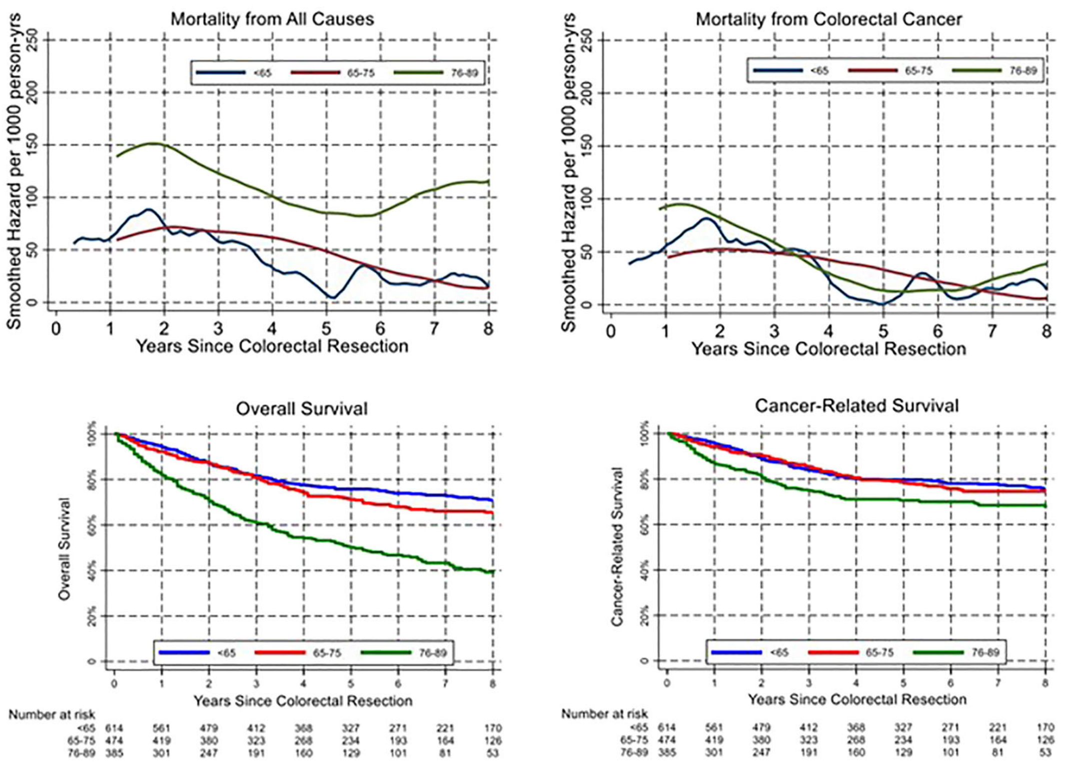


FIGURE 2
Temporal trend of all-cause and cancer-related mortality (upper panels) and corresponding overall and cancer-related survival (lower panels).

as part of the Enhanced Recovery After Surgery (ERAS) protocol could play a role in the optimization of elderly CRC patients, and it may contribute to better surgical results (28). As previously published by our group, ERAS protocol can be safely applied to elderly patients undergoing laparoscopic colorectal resection with improvements in short-term postoperative outcomes (12).

In line with previous reports, we observed a higher proportion of advanced and early stages of CRC in younger patients (29). Conversely, elderly patients presented more often with stage II and stage III disease ($p < 0.001$). This finding may be due to a surgical selection bias, since more complex and aggressive treatments may have been offered to younger and healthier patients, while older patients with metastatic disease were directed towards palliative care. Similarly, less elderly patients underwent surgery for rectal cancer compared to the younger groups, whereas more elderly patients presented with right colon cancer ($p < 0.001$). This is in line with previous literature, which reports decreasing incidence of rectal cancer in patients aged >65 years (30).

In our cohort, OS differed significantly between age classes, as expected. On multivariable analysis, age remained a statistically relevant risk factor for OS, together with stage, presence of comorbidities, occurrence of postoperative complications, non-curative resection, inadequate lymphadenectomy, and neoadjuvant treatment. On the other hand, whereas CRS was lower in older patients (Supplementary Figure 2), age did not prove to be an independent prognostic factor on multivariable analysis. Interestingly, neoadjuvant treatment emerged as an independent negative prognostic factor for OS and CRS on multivariable analysis. This result may be explained by the association between neoadjuvant treatment and a more advanced disease at diagnosis (locally advanced rectal cancer or stage IV CRC). When analysing the trend in overall and cancer-related mortality, we observed a peak within 2 years from surgery in all age groups and more pronounced in elderly patients (Figure 2). These results are only partly in line with previous literature that identified an excess mortality at the first year after surgery (17). On the contrary, our results suggest a prolonged impact of surgery beyond the first year and the peak in mortality within 18 and 24 months after cancer surgery. As shown in Figure 3 with Kaplan–Meier estimates of all-cause and cancer-related deaths, younger patients with CRC die almost always due to cancer progression or treatment-related complications. Conversely, the curves for elderly patients diverge quite steeply right after the first year, suggesting more deaths from competing causes.

Interestingly, life expectancy at 80–84 years of age was similar between stage 0–I CRC patients and the general

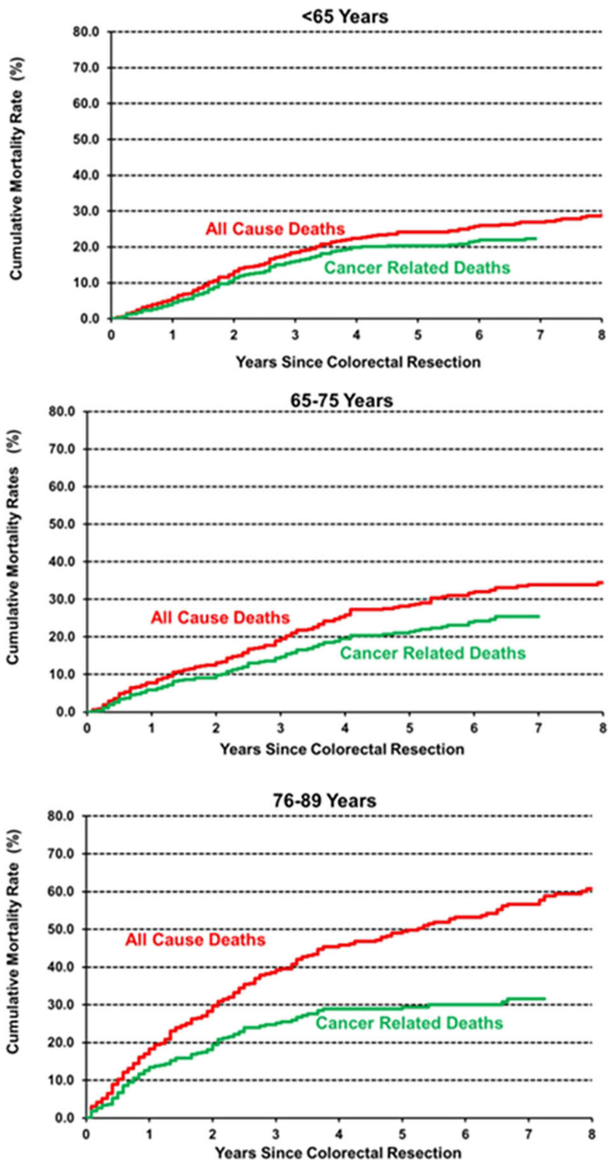


FIGURE 3
Cumulative incidence of all-cause and cancer-related mortality, estimated by the Kaplan–Meier method.

population of Verona (8.74 vs. 8.27 years, respectively, for men, 9.67 vs. 10.58 years for women), suggesting a low impact of surgical treatment. However, life expectancy of stage III and stage IV CRC was markedly reduced in both sexes. These data suggest that curative surgery can be safely performed also in elderly patients with CRC, with important benefits on OS if they do not die of competing causes and they present with resectable and early-stage disease. Palliative surgery or extensive resections for stage IV CRC, however, do not provide survival benefits.

From the results of our study and from current literature, we could conclude that elderly CRC patients should not be undertreated just because of their chronological age. A careful preoperative evaluation should select elderly fit patients for low-risk surgery. Frail and comorbid patients should otherwise be directed towards medical optimization and prehabilitation before surgery (31–33). The definition of frail patient is not unique: frailty may be defined as "a state of decreased physiologic reserve caused by the accumulation of ageing processes across multiple organ systems, which affects the patient's resistance to stressors" (34). Different tools for the assessment of frailty have been proposed, but they are often too time consuming to be routinely used in clinical practice (35, 36).

TABLE 2 Multivariate analysis for overall and cancer-related survival.

	Overall survival		Cancer-related survival	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age				
<65	1 (reference)		1 (reference)	
65-69	0.95 (0.54-1.67)	0.87	0.86 (0.45-1.66)	0.66
70-74	1.75 (1.06- 2.89)	**0.03**	1.54 (0.84-2.82)	0.16
75-79	2.00 (1.21-3.33)	**0.007**	1.59 (0.83-3.01)	0.16
80-84	4.39 (2.70-7.16)	**< 0.001**	1.99 (0.97-4.08)	0.06
85-89	4.36 (2.28-8.33)	**< 0.001**	1.66 (0.56-4.98)	0.36
Gender (male)	1.03 (0.75-1.41)	0.83	0.96 (0.64-1.44)	0.84
Tumour location				
Left colon	1 (reference)		1 (reference)	
Right colon	0.95 (0.65-1.37)	0.76	1.04 (0.62-1.74)	0.87
Rectum	0.89 (0.52-1.51)	0.66	0.92 (0.47-1.79)	0.81
Comorbidity (yes)	1.72 (1.12-2.66)	**0.01**	1.33 (0.81-2.18)	0.25
Type of surgery (urgent)	1.00 (0.46-2.03)	0.95	0.69 (0.21-2.32)	0.55
Postoperative complications (yes)	1.49 (1.09-2.03)	**0.01**	1.44 (0.96-2.15)	0.07
Stage				
Stage 0-1	1 (reference)		1 (reference)	
Stage 2	2.25 (1.39-3.64)	**0.001**	2.98 (1.43-6.23)	**0.004**
Stage 3	5.09 (3.08-8.42)	**< 0.001**	9.26 (4.48-19.13)	**< 0.001**
Stage 4	8.06 (3.99-16.28)	**< 0.001**	13.14 (5.28-32.69)	**< 0.001**
Potentially curative (R0-1)	0.29 (0.16-0.54)	**< 0.001**	0.25 (0.13-0.49)	**< 0.001**
Number of retrieved lymph-nodes <12	1.73 (1.34-2.64)	**0.01**	1.71 (1.00-2.92)	**0.001**
Neo-adjuvant therapy (yes)	2.09 (1.18-3.69)	**0.01**	2.82 (1.43-5.56)	**0.003**
Adjuvant therapy (yes)	0.69 (0.43-1.10)	0.12	0.67 (0.39-1.15)	0.15

p values – 0.05 were highlighted in bold.

Montroni et al. have recently proposed other more immediate tools to identify frail patients undergoing general surgery with a particular emphasis to assess the quality of life and the functional recovery after cancer surgery too (37, 38). However, all these scores focus on the identification of patients at risk for postoperative complications and short-term mortality, while they do not consider correlation with long-term mortality. Further studies are required to better define who could benefit from surgery and who should be spared because they are too frail and at risk of early mortality.

Despite including a large number of patients with a long follow-up time, our study presents some limitations. Due to its retrospective nature, it was not possible to retrieve complete data on some variables, including the administration of neoadjuvant/adjuvant therapy and the complications related to perioperative oncological treatment. Also, retrieval of the cause of the death was sometimes limited by the possibility to directly contact the patients or their relatives.

In conclusion, CRC surgery may be offered even to elderly patients with acceptable postoperative mortality. However, it should be considered that there is a more pronounced increase in 2-year all-cause mortality in elderly patients, suggesting a prolonged impact of surgery.

Data availability statement

The dataset will be available on reasonable request at the corresponding author. Requests to access the datasets should be directed to corrado.pedrazzani@univr.it.

Ethics statement

All methods used in this study were performed in accordance with the relevant ethical guidelines and regulations of the University Hospital of Verona, where the investigation was carried out. Informed consent was obtained from all patients and the study protocol was approved by the local ethical committee (ID: 1560 CESC).

Author contributions

GT, GC, CC, GV, and CP contributed to conception and design of the study. GT, GC, and LM organized the database. GC, LM, and GV performed the statistical analysis. GT, GC, CC, LM, EG, CP, and GV wrote the first draft of the manuscript. AR, AG, GV, and CP contributed to interpretation of the results and critical revision. All authors contributed to manuscript revision, read, and approved the submitted version.

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.2022.959650/full#supplementary-material

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al. *SEER cancer statistics review, 1975-2016*. (Bethesda, MD: National Cancer Institute) (2019).

2. Jung B, Påhlman L, Johansson R, Nilsson E. Rectal cancer treatment and outcome in the elderly: An audit based on the Swedish rectal cancer registry 1995-2004. *BMC Cancer* (2009) 9:68. doi: 10.1186/1471-2407-9-68

3. Samuelsson KS, Egenvall M, Klarin I, Lökk J, Gunnarsson U. Preoperative geriatric assessment and follow-up of patients older than 75 years undergoing elective surgery for suspected colorectal cancer. *J Geriatric Oncol* (2019) 10(5):709–15. doi: 10.1016/j.jgo.2019.01.020Al-Refaie

4. Al-Refaie WB, Parsons HM, Habermann EB, Kwaan M, Spencer MP, Henderson WG, et al. Operative outcomes beyond 30-day mortality: colorectal cancer surgery in oldest old. *Ann Surg* (2011) 253(5):947–52. doi: 10.1097/SLA.0b013e318216f56e

5. Chang GJ, Skibber JM, Feig BW, Rodriguez-Bigas M. Are we undertreating rectal cancer in the elderly? an epidemiologic study. *Ann Surg* (2007) 246(2):215–21. doi: 10.1097/SLA.0b013e318070838f

6. Janssen-Heijnen MLG, Maas HAAM, Saskia Houterman Lemmens VEPP, Rutten HJT, Coebergh JWW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer (Oxford Engl 1990)* (2007) 43(15):2179–93. doi: 10.1016/j.ejca.2007.06.008

7. Montroni I, Rostoft S, Spinelli A, Van Leeuwen BL, Ercolani G, Saur NM, et al. GOSAFE - Geriatric oncology surgical assessment and functional rEcovery after surgery: early analysis on 977 patients. *J Geriatric Oncol* (2020) 11(2):244–55. doi: 10.1016/j.jgo.2019.06.017

8. WHO. *Definition of an older or elderly person* (2010). Geneva: Switzerland World Health Organisation (Accessed 12/11/2013).

9. Jazwinski SM, Kim S. Examination of the dimensions of biological age. *Frontiers in genetics. Front Genet* (2019) 10:263. doi: 10.3389/fgene.2019.00263

10. Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut* (2011) 60(6):806–13. doi: 10.1136/gut.2010.232181

11. Byrne BE, Mamidanna R, Vincent CA, Faiz O. Population-based cohort study comparing 30- and 90-day institutional mortality rates after colorectal surgery. *Br J Surg* (2013) 100(13):1810–7. doi: 10.1002/bjs.9318

12. Pedrazzani C, Conti C, Turri G, Lazzarini E, Tripepi M, Scotton G, et al. Impact of age on feasibilty and short-term outcomes of ERAS after laparoscopic colorectal resection. *World J Gastrointest Surg* (2019) 11(10):395–406. doi: 10.5498/wjp.v2.i2.26

13. Gooiker GA, Dekker JWT, Bastiaannet E, van der Geest LGM, Merkus JWS, van de Velde CJH, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* (2012) 19(8):2428–34. doi: 10.1245/s10434-012-2294-6

14. Visser BC, Keegan H, Martin M, Wren SM. Death after colectomy: It's later than we think. *Arch Surg* (2009) 144(11):1021–7. doi: 10.1001/archsurg.2009.197

15. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? *Color Dis* (2012) 14(10):1175–82. doi: 10.1111/j.1463-1318.2011.02859.x

16. Dekker JWT, van den Broek CBM, Bastiaannet E, van de Geest LGM, Tollenaar RAEM, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* (2011) 18(6):1533–9. doi: 10.1245/s10434-011-1671-x

17. Dekker JWT, Gooiker GA, Bastiaannet E, van den Broek CBM, van der Geest LGM, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; A prolonged impact of the surgery in elderly colorectal cancer patients". *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2014) 40(11):1481–7. doi: 10.1016/j.ejso.2014.05.010

18. Janssen-Heijnen MLG, Houterman S, Lemmens VEPP, Louwman MWK, Coebergh JWW. Age and co-morbidity in cancer patients: A population-based approach. *Cancer Treat Res* (2005) 124:89–107. doi: 10.1007/0-387-23962-6_5

19. Bojer AS, Roikjær O. Elderly patients with colorectal cancer are oncologically undertreated. *Eur J Surg Oncol* (2015) 41(3):421–5. doi: 10.1016/j.ejso.2014.10.065

20. Bahadoer RR, Bastiaannet E, Claassen YHM, van der Mark M, van Eycken E, Verbeeck J, et al. One-year excess mortality and treatment in surgically treated patients with colorectal cancer: A EURECCA European comparison. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2021) 47(7):1651–60. doi: 10.1016/j.ejso.2021.01.01

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* (1987) 40(5):373–83. doi: 10.1016/0021-9681(87)90171-8

22. Weiser MR. AJCC 8th edition: Colorectal cancer. *Ann Surg Oncol* (2018) 25 (6):1454–5. doi: 10.1245/s10434-018-6462-1

23. United Nations, Department of Economic and Social Affairs, Population Division. World population prospects. In: *The 2017 revision, key findings and advance tables* (2017) United Nations, New York.

24. Available at: https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf.

25. Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. *Int J Cancer* (2012) 131(7):1649–58. doi: 10.1002/ijc.26192

26. Ketelaers SHJ, Orsini RG, Burger JWA, Nieuwenhuijzen GAP, Rutten HJT. Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2019) 45(11):2052–8. doi: 10.1016/j.ejso.2019.06.017

27. Breugom AJ, Bastiaannet E, Dekker JWT, Wouters MWJM, van de Velde CJH, Liefers GJ., et al. Decrease in 30-day and one-year mortality over time in patients aged ≥75 years with stage I-III colon cancer: A population-based study. *Eur J Surg Oncol* (2018) 44(12):1889–93. doi: 10.1016/j.ejso.2018.08.010

28. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced recovery after surgery (ERAS®) society recommendations: 2018. *World J Surg* (2019) 43(3):659–95. doi: 10.1007/s00268-018-4844-y

29. Chou CL, Chang SC, Lin TZ, Chen WS, Jiang JK, Wang HS, et al. Differences in clinicopathological characteristics of colorectal cancer between younger and elderly patients: An analysis of 322 patients from a single institution. *Am J Surg* (2011) 202(5):574–82. doi: 10.1016/j.amjsurg.2010.10.014

30. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal cancer incidence patterns in the united states, 1974-2013. *J Natl Cancer Inst* (2017) 109(8):djw322. doi: 10.1093/jnci/djw32

31. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: A call to action. *J Am Med Directors Assoc* (2013) 14(6):392–7. doi: 10.1016/j.jamda.2013.03.022

32. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: A randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* (2014) 121(5):937–47. doi: 10.1097/ALN.0000000000000393

33. Carli F, Minnella EM. Preoperative functional assessment and optimization in surgical patient: changing the paradigm. *Minerva Anestesiol* (2017) 83(2):214–8. doi: 10.23736/S0375-9393.16.11564-0

34. Balducci L. Aging, frailty, and chemotherapy. *Cancer Control* (2007) 14 (1):7–12. doi: 10.1177/107327480701400102

35. Monfardini S, Balducci L. A comprehensive geriatric assessment (CGA) is necessary for the study and the management of cancer in the elderly. *Eur J Cancer* (1999) 35(13):1771–2. doi: 10.1016/s0959-8049(99)00227-0

36. Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen HO, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Crit Rev Oncology/Hematology* (2010) 76 (3):208–17. doi: 10.1016/j.critrevonc.2009.11.002

37. Montroni I, Ugolini G, Saur NM, Spinelli A, Rostoft S, Millan M, et al. Personalized management of elderly patients with rectal cancer: Expert recommendations of the European society of surgical oncology, European society of coloproctology, international society of geriatric oncology, and American college of surgeons commission on cancer. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2018) 44(11):1685–702. doi: 10.1016/j.ejso.2018.08.003

38. Montroni I, Ugolini G, Saur NM, Rostoft S, Spinelli S, Van Leeuwen BL, et al. Quality of life in older adults after major cancer surgery: The GOSAFE international study. *J Natl Cancer Institute* (2022) 114:djac071. doi: 10.1093/jnci/djac071

TYPE Systematic Review
PUBLISHED 23 November 2022
DOI 10.3389/fonc.2022.1066417

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Andrea Costanzi,
ASST Lecco, Italy
Imerio Angriman,
University of Padua, Italy

*CORRESPONDENCE
Jiarong Lan
sdwaters@126.com

[†]These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 17 October 2022
ACCEPTED 08 November 2022
PUBLISHED 23 November 2022

CITATION
Mao Y and Lan J (2022) Prognostic value of the geriatric nutritional index in colorectal cancer patients undergoing surgical intervention: A systematic review and meta-analysis. *Front. Oncol.* 12:1066417.
doi: 10.3389/fonc.2022.1066417

Prognostic value of the geriatric nutritional index in colorectal cancer patients undergoing surgical intervention: A systematic review and meta-analysis

Yiqing Mao[1†] and Jiarong Lan[2,3*†]

[1]Department of Gastrointestinal Surgery, Huzhou Central Hospital, Affiliated Central Hospital Huzhou University, Huzhou, China, [2]School of Basic Medical Sciences, Zhejiang Chinese Medical University, Hangzhou, China, [3]Department of Medicine, Huzhou Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, Huzhou, China

Background: We reviewed the literature to assess the prognostic ability of the geriatric nutritional risk index (GNRI) for patients with colorectal cancer (CRC) undergoing curative surgery.

Methods: The online databases of PubMed, CENTRAL, ScienceDirect, Embase, and Google Scholar were searched for articles reporting the relationship between GNRI and outcomes in CRC patients. English language studies were searched up to 28th April 2022.

Results: Ten studies with 3802 patients were included. Meta-analysis indicated that patients with low GNRI had significantly poor overall survival (HR: 2.41 95% CI: 1.72, 3.41 $I^2 = 68\%$) and disease-free survival (HR: 1.92 95% CI: 1.47, 2.49 $I^2 = 49\%$) as compared to those with high GNRI. The meta-analysis also indicated a significantly higher risk of complications with low GNRI as compared to high GNRI (HR: 1.98 95% CI: 1.40, 2.82 $I^2 = 0\%$). The results did not change on subgroup analysis based on study location, age group, GNRI cut-off, and sample size.

Conclusion: Current evidence indicates that GNRI can be a valuable prognostic indicator for CRC patients undergoing surgical intervention. Patients with low GNRI have poor overall and disease-free survival and a higher incidence of complications. Clinicians could use this simple indicator to stratify patients and formulate personalized treatment plans.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier (CRD42022328374).

KEYWORDS

nutrition, prognosis, survival, complications, cancer

Introduction

Cancer has become the most common cause of mortality worldwide. Amongst the numerous subtypes, colorectal cancer (CRC) ranks the 2nd most prevalent cancer in females and 3rd most common malignancy amongst men around the globe (1). The prevalence has been high in Asian populations but a large number of patients are also being detected in Western regions and developing nations (2). CRC is known to have a predilection for the older age group as the median age of diagnosis is reported to be 67 years (3). Western data indicate that of the approximately 140,000 confirmed cases of CRC detected in 2018, around 60% were elderly with an age of >65 years. Furthermore, older adults accounted for almost 70% of mortality cases in the same period (4). Identification of modifiable risk factors for poor prognosis can aid in appropriate treatment planning and improve the long-term overall survival (OS) and disease-free survival (DFS) of CRC patients. Of the numerous risk factors identified, malnutrition has been one of the most prominent and well-defined factors associated with poor survival after CRC (5). However, there has been no consensus in the literature on how to measure malnutrition to best assess the prognosis of such patients (6). Several measurement indices like the body mass index, bodyweight loss, serum albumin levels, psoas muscle area, mini-nutritional assessment, prognostic nutritional index, and controlling nutritional status score have been used to quantify malnutrition in a cancer patient (7, 8). Since >50% of patients with gastrointestinal (GI) cancer suffer from malnutrition, there is a need for an easy to calculate and robust malnutrition indicator which has a good prognostic ability (7). The Geriatric Nutritional Risk Index (GNRI) is a simple malnutrition screening tool estimated from serum albumin levels and ideal body weight (9). It has been used in literature to assess the prognosis of patients undergoing percutaneous coronary interventions, and hemodialysis as well as for those with heart and respiratory diseases (10–13). The tool has also received attention in the field of oncology with several studies reporting its use for different cancers (14–16). Recently, Xie et al (17) have reviewed the ability of GNRI to predict the prognosis of patients with GI malignancies. In a pooled analysis of nine studies, the authors reported that patients with low GNRI had a significantly higher risk of complications and poor long-term survival as compared to those with high GNRI. An important limitation of their review was patients with different GI cancer were pooled in a single meta-analysis. Over the past few years, several authors (18–20) have reported their experience with the use of GNRI for CRC patients but there has been no consolidated review to examine the available evidence. Given this deficiency in literature, we present the results of the first systematic review and meta-analysis examining the prognostic ability of GNRI for CRC patients undergoing curative surgical resection.

Material and methods

Search and eligibility

The review was pre-registered on PROSPERO (No CRD42022328374). The PRISMA recommendations were used during the reporting of the review (21). A detailed search on the online databases of PubMed, CENTRAL, ScienceDirect, Embase, and Google Scholar was conducted for articles reporting the prognostic ability of GNRI for CRC patients. The search was last done on 28th April 2022. Two reviewers were independently involved in the search which was restricted to English-language publications only. The search terms were; "colorectal cancer", "rectal cancer", "geriatric nutritional risk index", "prognosis", "nutrition", and "survival". The search was conducted by combining the search terms with Boolean operators "OR" and "AND". Details can be found in Supplementary Table 1. The search results combined for initial titles and abstract screening. Only studies relevant to the review were extracted and matched against the eligibility criteria. The entire procedure involved two reviewers working independently.

The eligibility criteria were all types of studies reporting the relationship between GNRI and outcomes of CRC patients undergoing curative resections. The outcomes were OS, DFS, and/or complications. We excluded studies 1) not reporting data for CRC patients separately 2) not on patients undergoing surgical intervention 3) not reporting any of the relevant outcomes 4) studies with duplicate data. If there were two studies from the same center conducted during the same period the article with the largest sample was to be included.

In the final stage, the full-text articles were screened based on the eligibility criteria, and those fulfilling the same were included. Any differences in study selection were resolved by discussion. Lastly, we also hand-searched the reference list of included studies and previous reviews to look for any missed articles.

Data management

Using an Excel spreadsheet the following data were extracted from the included studies: Details of study authors, publication year, study location, study type, inclusion criteria, the cut-off for GNRI, sample size, age, gender, carcinoembryonic antigen (CEA) levels, location of cancer (colon or rectal), tumor invasion, presence of lymph node metastasis, use of adjuvant therapy, follow-up and outcomes. The outcomes assessed in the review were OS, DFS, and complications. We assessed the risk of bias using the Newcastle-Ottawa scale (NOS) (22).

Statistical analysis

The prognostic ability of GNRI was reported as multivariable-adjusted hazard ratios (HR) by most studies. These were extracted and combined in a random-effects model to calculate the total effect size as HR with 95% confidence intervals (CI). We assessed inter-study heterogeneity using the I^2 statistic. Publication bias was examined by visual inspection of funnel plots and a sensitivity analysis was also performed. Subgroup analysis was carried out based on study location (Japanese vs non-Japanese), age group included (≥65 years, ≥75 years, and others), GNRI cut-off (98 and others), and sample size (>300 and <300). Results were reported in tabular format. Funnel plots, sensitivity analysis, and subgroup analysis was not conducted for complication rates due to limited data. For studies not reporting outcomes as adjusted ratios, a descriptive analysis was undertaken. The data analysis was conducted using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014).

Results

The initial search resulted in 5499 articles (Figure 1). After deduplication, 2328 articles were screened by the reviewers. 25 of these were selected for further analysis. Finally, ten studies were deemed eligible for inclusion in the review (18–20, 23–29).

All included studies were retrospective observational studies conducted in Asian countries (Table 1). Most of them were carried out in the Japanese population. One was from Taiwan and another study was from China. The number of participants in the studies ranged from 80 to 1206. The total pooled sample size was 3802 patients. Most studies included all elderly patients with CRC undergoing curative resection. However, there were some exceptions. One study included patients only with locally advanced rectal cancer, while another included individuals only with stage Tis/T1 CRC undergoing endoscopic submucosal dissection, and one study included those with CRC liver metastasis. The percentage of male patients ranged from 44 to 79.6% in the included studies while the proportion of patients

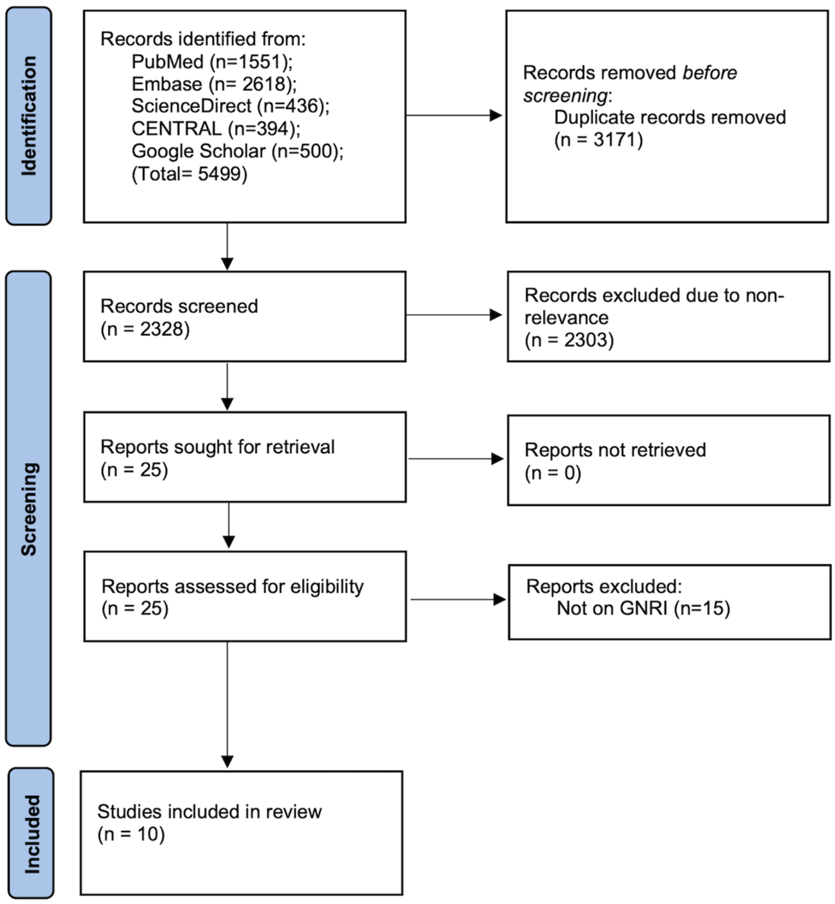


FIGURE 1
Details of literature search in the PRISMA flow-chart.

TABLE 1 Details of included studies.

Study	Study Location	Patients	Cut-off of GNRI	Groups	Sample size	Mean/ Median age (years)	Male gender (%)	CEA, ≥5 (%)	Location	T3-T4 stage (%)	Lymph node metastasis (%)	Adjuvant therapy (%)	Follow-up	NOS
Yagyu 2022 (29)	Japan	Elderly patients (≥75 years) with stage II CRC	93.465	High Low	147 201	81 83	46.9 45.8	NR	C 78.9%, R 21.1% C 79.6%, R 20.4%	9.5* 24.4	NR	12.9 10.9	Up to 5 years	8
Hayama 2022 (28)	Japan	Elderly patients (≥65 years) with stage I-III CRC	101.1	High Low	207 51	NR	43.4 44	34.5% 36%	C 19.7%, R 80.3% C 9.8%, R 90.2%	35.4 4	32.4 38	NR	Median 1214 days	8
Doi 2022 (27)	Japan	Patients with stage I-III CRC	98	High Low	190 139	71.4 76.9	44.7 45.3	32.8% 44.9%	NR	55.8 77.7	32.1 31.7	NR	Median 32.1 months	8
Liao 2021 (26)	Taiwan	Elderly patients (≥75 years) with stage I-III CRC	98	High Low	662 544	79.5 81.6	57.7 53.5	30.1% 40%	C 62.2%, R 37.8% C 73.7%, R 26.3%	75.4 86.4	39.9 42	NR	Median 60.7 months	8
Kato 2021 (24)	Japan	Elderly patients (≥75 years) with Tis/T1 CRC undergoing ESD	96.3	NR	691	NR	NR	NR	NR	NR	NR	NR	Median 41-46 months	7
Kataoka 2021 (25)	Japan	Elderly patients (≥65 years) with CRC	98	High Low	127 127	75.3 74.9	51.2 52.8	48.8% 48%	C 65.4%, R 34.6% C 66.1%, R 33.9%	NR	NR	NR	Up to 5 years	8
Ide 2021 (20)	Japan	Patients with locally advanced rectal cancer undergoing CRT	104.25	High Low	55 38	NR	72.7 73.7	47.3% 60.5%	R 100% R 100%	NR	NR	42 23	Median 60.03 months	8
Tang 2020 (23)	China	Elderly patients (≥65 years) with CRC	98	High Low	117 113	NR	54.7 79.6	37.6% 35.4%	C 45.3%, R 54.7% C 54.9%, R 45.1%	68.4 69	NR	NR	Median 61 months	8
Sasaki 2020 (19)	Japan	Elderly patients (≥65 years) with CRC	98	High Low	176 137	NR	70.5 56.2	28.9% 35.4%	C 77.8%, R 33.2% C 74.5%, R 35.5%	49.4 48.2	26.7 29.9	NR	Median 60.5 months	8
Iguchi 2020 (18)	Japan	Patients with stage CRC and synchronous liver metastasis	98	High Low	50 30	62.4 65.5	52 60	NR	NR	88 90	NR	75.5 69	Mean 1545 days	8

*only T4 stage.
CRC, colorectal cancer; CEA, Carcinoembryonic antigen; GNRI, Geriatric Nutritional Risk Index; C, colon; R, rectal; NR, not reported; NOS, Newcastle Ottawa scale.

10.3389/fonc.2022.1066417

with high CEA ranged from 28.9 to 48.8%. The distribution of colon and rectal cancer varied across included studies. Details on tumor invasion, lymph node metastasis, and the use of adjuvant therapy were not reported by all studies. All studies had a follow-up of more than 1 year. The NOS score ranged from 7 to 8.

Eight studies reported data on OS. Meta-analysis indicated that patients with low GNRI had significantly poor OS as compared to those with high GNRI (HR: 2.41 95% CI: 1.72, 3.41 $I^2 = 68\%$) (Figure 2). The results remained the same on the sequential exclusion of studies during the sensitivity analysis. We did not note any publication bias on the visual inspection of the funnel plot (Figure 3).

Data on DFS was available only from six studies. On pooled analysis, we noted that low GNRI was a significant predictor of poor DFS in CRC patients (HR: 1.92 95% CI: 1.47, 2.49 $I^2 = 49\%$) (Figure 4). There was no change in the significance of the results on sensitivity analysis. There was no evidence of publication bias noted on the funnel plot (Figure 5).

Only three studies assessed the prognostic ability of GNRI for predicting complications. Meta-analysis indicated a significantly higher risk of complications with low GNRI as compared to high GNRI (HR: 1.98 95% CI: 1.40, 2.82 $I^2 = 0\%$) (Figure 6).

The results of subgroup analysis for OS and DFS are reported in Table 2. We noted that subgroup analysis for the outcome OS based on study location, GNRI cut-off, and sample size did not change the significance of the results. However, GNRI was not predictive of OS on a pooled analysis of two studies including only those with ≥75 years of age. The results of the outcome DFS did not change on subgroup analysis based on study location, age group, GNRI cut-off, and sample size.

Only one study by Kataoka et al (25) did not report outcomes as adjusted ratios and hence could not be included in the meta-analysis. In their study, the authors used propensity score matching to compare data of patients with low and high GNRI (cut-off 98). Patients with low GNRI had significantly poor OS (p=0.002), DFS (p=0.006), and a higher rate of complications (p=0.001) as compared to those with high GNRI.

Discussion

Cancer patients have a high prevalence of malnutrition and muscle wasting which is known to negatively affect survival and increase the length of hospital stays. Indeed, the catabolic and physiological impact of cancer cachexia escalates the nutritional and energy requirement of the individual but it is seldom met due to inadequate dietary intake and reduced physical activity (5). Malnutrition is further exacerbated in GI malignancies due to additional factors like malabsorption, obstructive syndrome, and diarrhea (7). Research has shown that malnutrition is unexpectedly high in patients with GI malignancies with clinicians recognizing only 1 out of 4 patients with malnutrition leading to inadequate pretreatment nutritional support and poor outcomes. This illustrates the fact that nutritional screening is of utmost importance even when the patient shows no overt signs of malnutrition (30). One of the limitations of various nutritional screening tools is their varying sensitivity and specificities. Ideally, the screening tool should be simple, brief, inexpensive, with high sensitivity and good specificity (31).

In this context, the GNRI was developed by Bouillanne et al. in 2005 as a simple tool to predict outcomes in elderly patients using albumin and body weight data (9). Since then the tool has been used to predict outcomes in a variety of patients (10–13). Several meta-analysis studies have reported the predictability of GNRI for various cancer subtypes. Wang et al (32) in a meta-analysis of eight studies have shown that low GNRI is associated with poor OS (HR: 1.99, 95% CI: 1.68-2.35) and DFS (HR = 2.34, 95% CI: 1.11-4.95) in patients with non-small cell lung cancer. In another recent meta-analysis, Yu et al (33) compiled data from 14 studies and noted that low pretreatment GNRI predicted poor OS (HR = 1.47, 95% CI: 1.33-1.63) and DFS (HR = 1.69, 95% CI: 1.24-2.31) in patients with esophageal cancer. Individual studies have shown that GNRI could predict outcomes in patients with head and neck cancer, renal cancer, pancreatic cancer, and gastric cancer (14, 16, 34, 35). However, since each cancer subtype is different, it is important that the predictability of GNRI is established for CRC as well.

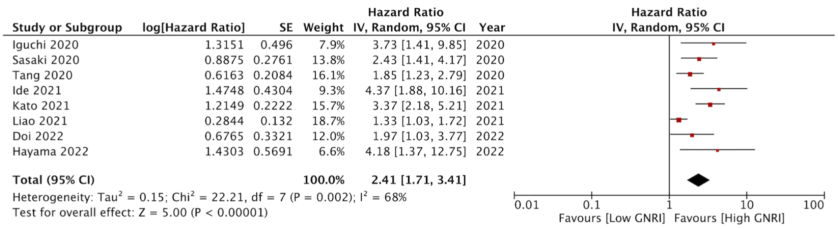


FIGURE 2
Forest plot of the prognostic ability of GNRI for OS in CRC patients.

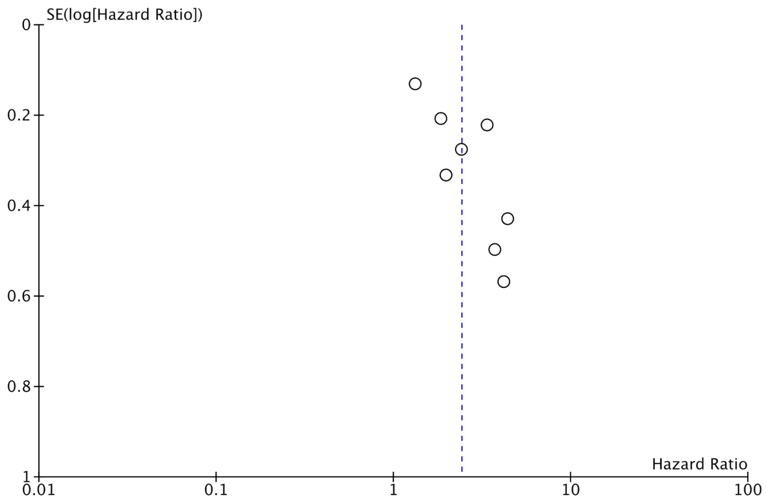


FIGURE 3
Funnel plot for the meta-analysis on the prognostic ability of GNRI for OS in CRC patients.

We conducted a detailed literature search to recognize ten studies with a total of 3802 cancer patients undergoing curative surgical resection for CRC. This provided a more homogenous group of patients undergoing the same primary treatment unlike the previous meta-analysis wherein patients with different GI malignancies undergoing different treatments were included (17). On pooled analysis, it was seen that patients with low GNRI had a 2.4 times increased risk of the poor OS as compared to those with high GNRI. Secondly, patients with low GNRI had 1.9 times increased risk of recurrence as compared to those with high GNRI. We also noted that low GNRI was significantly associated with higher rates of complications, albeit with only three studies in the meta-analysis. On examination of all three forest plots of our meta-analysis, it can be seen that the direction of the result was consistent across all studies only with varying 95% CI. None of the studies noted a non-significant association between low GNRI and outcomes in CRC patients. There was little evidence of publication bias and the survival results maintained their significance on sensitivity analysis. The results were robust and thereby increase the validity of our conclusions.

An important limitation of the meta-analysis was the moderate heterogeneity in the meta-analysis of OS and DFS. This could be due to several known and unknown variables like sample size, study location, patient demographics, baseline stage of CRC, treatment protocols, and cut-off used for GNRI. Based on the availability of data we divided the studies into separate groups based on sample size, study location, age group included, and the cut-off for GNRI only to note no change in the significance of the results. The exception was the outcome of OS in the subgroup of studies including only patients aged ≥75years. The overall effect size was 2.08 with a 95% CI of 0.84, 5.17. The non-significant results could be due to the small number of studies in the analysis as the 95% CI was wide with the lower end very close to 1 and the upper end indicating a 5 times increased risk of poor OS.

If the GNRI has to be incorporated into clinical practice, a well-established cut-off is needed to segregate patients into low and high GNRI groups. Most of the studies in our review as well as in literature (15, 33) have used the cut-off of 98 for classifying patients into those with low and high GNRI. Nevertheless, there

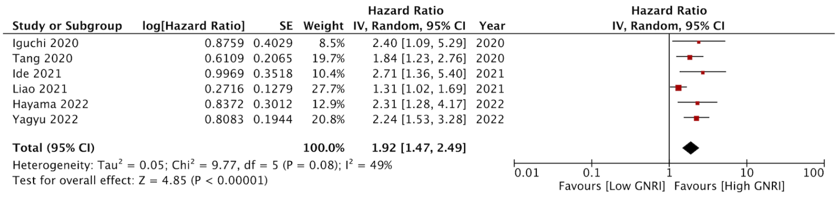


FIGURE 4
Forest plot of the prognostic ability of GNRI for DFS in CRC patients.

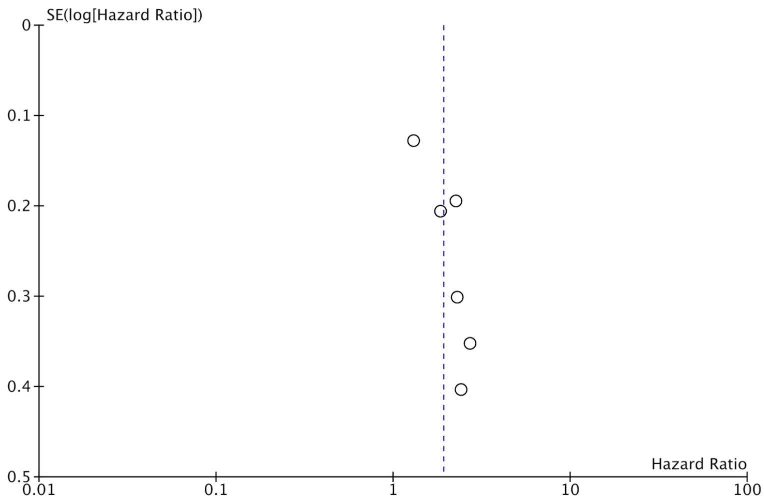


FIGURE 5
Funnel plot for the meta-analysis on the prognostic ability of GNRI for DFS in CRC patients.

has been no consensus and other cut-offs have been used by studies based on receiver operating curve analysis of population-specific data. In our subgroup analysis, we noted that the results were the same for studies using a cut-off of 98 or any other for assessing the prognosis of CRC patients. Future studies should focus on GNRI cut-off in different populations to arrive at a common figure for clinical practice.

The good prognostic ability of GNRI could be due to its combined use of two important markers of malnutrition: albumin and body weight (9). Low serum albumin levels have been congruous with malnutrition and hypoalbuminemia has been associated with poor wound healing, infections, and reduced survival in cancer patients. Serum albumin has an immunomodulatory role with low levels leading to reduced cell-mediated immunity against cancer cells (5). Hypoalbuminemia causes reduced macrophage activation and granuloma formation which may promote surgical site infections and other complications in CRC patients (6). Hu et al (5) in a study on 30676 CRC patients have found a statistically significant association between low albumin levels and postoperative complications like venous thromboembolism, surgical site infections, pneumonia, septic shock, prolonged ventilator use, blood transfusion, return to the operating room, stroke, and re-intubation in CRC patients. Secondly, the GNRI uses a ratio of current body weight to ideal body weight as a marker of the body mass index (BMI) of the patients. Cancer patients with low BMI are at an increased risk of poor survival (36). Thus, it can be postulated that the combination of albumin and body weight increases the ability of the GNRI to predict prognosis in cancer patients.

There are several strengths to our review. It is the first meta-analysis to aggregate evidence on the role of GNRI in predicting outcomes in CRC patients. We attempted to include a homogenous population of patients undergoing surgical intervention. The validity of the results was tested by sensitivity and different subgroup analyses.

Nevertheless, there are some limitations as well. Not all studies provided data for all three outcomes. Hence, the number of studies in the meta-analysis was less than 10. Secondly, not all studies were of large sample size and this may have reduced the power of our analysis. Thirdly, there was some heterogeneity in the study population included in the studies. Some included only patients with T1 stage while another included patients with liver

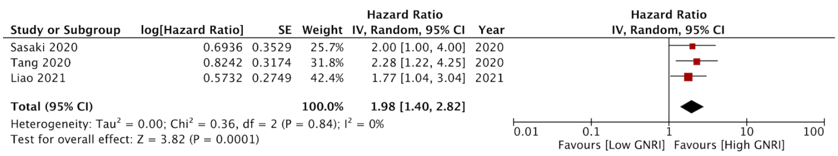


FIGURE 6
Forest plot of the prognostic ability of GNRI for complications in CRC patients.

TABLE 2 Subgroup analysis.

Variable	Groups	Number of studies	Hazard ratio
OS			
Study location	Japanese	6	2.98 (95%CI: 2.29, 3.89 I^2 = 0%)
	Non-Japanese	2	1.51 (95%CI: 1.10, 2.07 I^2 = 45%)
Age group included	≥65 years only	3	2.17 (95%CI: 1.57, 3.00 I^2 = 3%)
	≥75 years only	2	2.08 (95%CI: 0.84, 5.17 I^2 = 92%)
	Others	3	2.93 (95%CI: 1.74, 4.93 I^2 = 21%)
GNRI cut-off	98	5	1.86 (95%CI: 1.37, 2.54 I^2 = 50%)
	Others	3	3.62 (95%CI: 2.51, 5.22 I^2 = 0%)
Sample size	>300	4	2.11 (95%CI: 1.29, 3.45 I^2 = 79%)
	<300	4	2.91 (95%CI: 1.75, 4.86 I^2 = 42%)
DFS			
Study location	Japanese	4	2.34 (95%CI: 1.79, 3.08 I^2 = 0%)
	Non-Japanese	2	1.50 (95%CI: 1.08, 2.07 I^2 = 49%)
Age group included	≥65 years only	2	1.98 (95%CI: 1.42, 2.77 I^2 = 0%)
	≥75 years only	2	1.68 (95%CI: 1.00, 2.84 I^2 = 81%)
	Others	2	2.57 (95%CI: 1.53, 4.32 I^2 = 0%)
GNRI cut-off	98	3	1.60 (95%CI: 1.16, 2.19 I^2 = 42%)
	Others	3	2.34 (95%CI: 1.75, 3.12 I^2 = 0%)
Sample size	>300	2	1.68 (95%CI: 1.00, 2.84 I^2 = 81%)
	<300	4	2.14 (95%CI: 1.61, 2.83 I^2 = 0%)

OS, overall survival; DFS, disease free survival; GNRI, Geriatric Nutritional Risk Index; CI, confidence intervals.

metastasis. The effect of such variation could be assessed only by sensitivity analysis and not by subgroup analysis. Fourthly, all studies were on Asian populations with most studies from Japan. Thus the results cannot be generalized to other populations.

Conclusions

Current evidence indicates that GNRI can be a valuable prognostic indicator for CRC patients undergoing surgical intervention. Patients with low GNRI have poor OS, DFS, and a higher incidence of complications. Clinicians could use this simple indicator to stratify patients and formulate personalized treatment plans. Further studies with a larger sample size are required to validate the results in non-Asian populations and obtain the most optimal cut-off to predict outcomes.

Data availability statement

Publicly available datasets were analyzed in this study. 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

YM and JL conceived and designed the study. YM and JL were involved in literature search and data collection. YM analyzed the data. JL wrote the paper. and JL reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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.2022.1066417/full#supplementary-material

References

1. Pérez-Escalante E, Cariño-Cortés R, Fernández-Martínez E, Ortiz MI, Muñoz-Pérez VM, Sánchez-Crisóstomo I, et al. Colorectal cancer: Causes and evidence of chemopreventive treatments. *Curr Pharm Biotechnol* (2018) 19:1135–55. doi: 10.2174/1389201020666181226112712

2. Brenner H, Chen C. The colorectal cancer epidemic: challenges and opportunities for primary, secondary and tertiary prevention. *Br J Cancer* (2018) 119:785–92. doi: 10.1038/S41416-018-0264-X

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2018) 68:394–424. doi: 10.3322/CAAC.21492

4. Papamichael D, Hernandez P, Mistry R, Xenophontos E, Kakani C. Adjuvant chemotherapy in patients with colorectal cancer. is there a role in the older adult? *Eur J Surg Oncol* (2020) 46:363–8. doi: 10.1016/J.EJSO.2020.01.002

5. Hu WH, Eisenstein S, Parry L, Ramamoorthy S. Preoperative malnutrition with mild hypoalbuminemia associated with postoperative mortality and morbidity of colorectal cancer: a propensity score matching study. *Nutr J* (2019) 18:33. doi: 10.1186/S12937-019-0458-Y

6. Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. *Nutr J* (2015) 14:91. doi: 10.1186/S12937-015-0081-5

7. Benoist S, Brouquet A. Nutritional assessment and screening for malnutrition. *J Visc Surg* (2015) 152 Suppl 1:S3–7. doi: 10.1016/S1878-7886(15)30003-5

8. Kubota T, Shoda K, Konishi H, Okamoto K, Otsuji E. Nutrition update in gastric cancer surgery. *Ann Gastroenterol Surg* (2020) 4:360–8. doi: 10.1002/AGS3.12351

9. Bouillanne O, Morineau G, Dupant C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* (2005) 82:777–83. doi: 10.1093/AJCN/82.4.777

10. Takahashi H, Ito Y, Ishii H, Aoyama T, Kamoi D, Kasuga H, et al. Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients. *J Cardiol* (2014) 64:32–6. doi: 10.1016/J.JJCC.2013.10.018

11. Wada H, Dohi T, Miyauchi K, Doi S, Naito R, Konishi H, et al. Prognostic impact of the geriatric nutritional risk index on long-term outcomes in patients who underwent percutaneous coronary intervention. *Am J Cardiol* (2017) 119:1740–5. doi: 10.1016/J.AMJCARD.2017.02.051

12. Li H, Cen K, Sun W, Feng B. Prognostic value of geriatric nutritional risk index in elderly patients with heart failure: a meta-analysis. *Aging Clin Exp Res* (2021) 33:1477–86. doi: 10.1007/S40520-020-01656-3

13. Matsumura T, Mitani Y, Oki Y, Fujimoto Y, Ohira M, Kaneko H, et al. Comparison of geriatric nutritional risk index scores on physical performance among elderly patients with chronic obstructive pulmonary disease. *Heart Lung* (2015) 44:534–8. doi: 10.1016/J.HRTLNG.2015.08.004

14. Sakamoto T, Yagyu T, Uchinaka E, Miyatani K, Hanaki T, Kihara K, et al. The prognostic significance of combined geriatric nutritional risk index and psoas muscle volume in older patients with pancreatic cancer. *BMC Cancer* (2021) 21:342. doi: 10.1186/S12885-021-08094-Y

15. Matsuura S, Morikawa K, Ito Y, Kubota T, Ichijo K, Mochizuki E, et al. The geriatric nutritional risk index and prognostic nutritional index predict the overall survival of advanced non-small cell lung cancer patients. *Nutr Cancer* (2021) 74:1606–13. doi: 10.1080/01635581.2021.1960387

16. Nakayama M, Gosho M, Adachi M, Ii R, Matsumoto S, Miyamoto H, et al. The geriatric nutritional risk index as a prognostic factor in patients with advanced head and neck cancer. *Laryngoscope* (2021) 131:E151–6. doi: 10.1002/LARY.28587

17. Xie H, Tang S, Wei L, Gan J. Geriatric nutritional risk index as a predictor of complications and long-term outcomes in patients with gastrointestinal malignancy: a systematic review and meta-analysis. *Cancer Cell Int* (2020) 20:530. doi: 10.1186/S12935-020-01628-7

18. Iguchi T, Sugimachi K, Mano Y, Motomura T, Sugiyama M, Ota M, et al. Prognostic impact of geriatric nutritional risk index in patients with synchronous colorectal liver metastasis. *Anticancer Res* (2020) 40:4165–71. doi: 10.21873/ANTICANRES.14416

19. Sasaki M, Miyoshi N, Fujino S, Ogino T, Takahashi H, Uemura M, et al. The geriatric nutritional risk index predicts postoperative complications and prognosis in elderly patients with colorectal cancer after curative surgery. *Sci Rep* (2020) 10:10744. doi: 10.1038/S41598-020-67285-Y

20. Ide S, Okugawa Y, Omura Y, Yamamoto A, Ichikawa T, Kitajima T, et al. Geriatric nutritional risk index predicts cancer prognosis in patients with local advanced rectal cancer undergoing chemoradiotherapy followed by curative surgery. *World J Surg Oncol* (2021) 19:34. doi: 10.1186/S12957-021-02139-Z

21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* (2021) 88:105906. doi: 10.1016/j.ijsu.2021.105906

22. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses* . Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed October 30, 2020).

23. Tang S, Xie H, Kuang J, Gao F, Gan J, Ou H. The value of geriatric nutritional risk index in evaluating postoperative complication risk and long-term prognosis in elderly colorectal cancer patients. *Cancer Manag Res* (2020) 12:165–75. doi: 10.2147/CMAR.S234688

24. Kato M, Hayashi Y, Fukuda H, Yamaguchi S, Inoue T, Ogiyama H, et al. Geriatric nutritional risk index as a prognostic indicator in elderly patients with early colorectal cancer undergoing endoscopic submucosal dissection. *Dig Endosc* (2022) 34:569–78. doi: 10.1111/DEN.14090

25. Kataoka M, Hirano Y, Ishii T, Ishikawa S, Kataoka A, Fujii T, et al. Prognostic utility of geriatric nutritional risk index after curative resection of colorectal cancer: A propensity score-matched study. *Cancer Diagnosis Progn* (2021) 1:479–84. doi: 10.21873/cdp.10064

26. Liao CK, Chern YJ, Hsu YJ, Lin YC, Yu YL, Chiang JM, et al. The clinical utility of the geriatric nutritional risk index in predicting postoperative complications and long-term survival in elderly patients with colorectal cancer after curative surgery. *Cancers (Basel)* (2021) 13:5852. doi: 10.3390/CANCERS13225852

27. Doi S, Migita K, Ueno M, Yasuda S, Aoki S, Fujimoto K, et al. The prognostic significance of the geriatric nutritional risk index in colorectal cancer patients. *Nutr Cancer* (2022) 74:2838–45. doi: 10.1080/01635581.2022.2036768

28. Hayama T, Hashiguchi Y, Ozawa T, Watanabe M, Fukushima Y, Shimada R, et al. The preoperative geriatric nutritional risk index (GNRI) is an independent prognostic factor in elderly patients underwent curative resection for colorectal cancer. *Sci Rep* (2022) 12:3682. doi: 10.1038/S41598-022-07540-6

29. Yagyu T, Yamamoto M, Tanio A, Hara K, Sugezawa K, Uejima C, et al. Risk factors for recurrence in elderly patients with stage II colorectal cancer: a multicenter retrospective study. *BMC Cancer* (2022) 22:390. doi: 10.1186/S12885-022-09501-8

30. Attar A, Malka D, Sabaté JM, Bonnetain F, Lecomte T, Aparicio T, et al. Malnutrition is high and underestimated during chemotherapy in gastrointestinal cancer: an AGEO prospective cross-sectional multicenter study. *Nutr Cancer* (2012) 64:535–42. doi: 10.1080/01635581.2012.670743

31. Håkonsen SJ, Pedersen PU, Bath-Hextall F, Kirkpatrick P. Diagnostic test accuracy of nutritional tools used to identify undernutrition in patients with colorectal cancer: a systematic review. *JBI Database Syst Rev Implement Rep* (2015) 13:141–87. doi: 10.11124/JBISRIR-2015-1673

32. Wang H, Li C, Yang R, Jin J, Liu D, Li W. Prognostic value of the geriatric nutritional risk index in non-small cell lung cancer patients: A systematic review and meta-analysis. *Front Oncol* (2022) 11:794862. doi: 10.3389/FONC.2021.794862

33. Yu J, Zhang W, Wang C, Hu Y. The prognostic value of pretreatment geriatric nutritional risk index in esophageal cancer: A meta-analysis. *Nutr Cancer* (2022) 74:3202–10. doi: 10.1080/01635581.2022.2069273

34. Kang HW, Seo SP, Kim WT, Yun SJ, Lee SC, Kim WJ, et al. A low geriatric nutritional risk index is associated with aggressive pathologic characteristics and poor survival after nephrectomy in clear renal cell carcinoma: A multicenter retrospective study. *Nutr Cancer* (2020) 72:88–97. doi: 10.1080/01635581.2019.1621357

35. Furuke H, Matsubara D, Kubota T, Kiuchi J, Kubo H, Ohashi T, et al. Geriatric nutritional risk index predicts poor prognosis of patients after curative surgery for gastric cancer. *Cancer Diagnosis Progn* (2021) 1:43–52. doi: 10.21873/cdp.10007

36. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS study). *Cancer Epidemiol Biomarkers Prev* (2017) 26:1008–15. doi: 10.1158/1055-9965.EPI-17-0200

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 28 November 2022
DOI 10.3389/fonc.2022.1055418

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Paola Ciriaco,
San Raffaele Scientific Institute (IRCCS), Italy
Xiaomin Niu,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Filippo Tommaso Gallina
filippogallina92@gmail.com

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 27 September 2022
ACCEPTED 28 October 2022
PUBLISHED 28 November 2022

CITATION
Gallina FT, Tajè R, Forcella D, Gennari V, Visca P, Pierconti F, Coccia C, Cappuzzo F, Sperduti I, Facciolo F and Melis E (2022) Perioperative outcomes of robotic lobectomy for early-stage non-small cell lung cancer in elderly patients. *Front. Oncol.* 12:1055418. doi: 10.3389/fonc.2022.1055418

Perioperative outcomes of robotic lobectomy for early-stage non-small cell lung cancer in elderly patients

Filippo Tommaso Gallina[1*], Riccardo Tajè[1], Daniele Forcella[1], Valeria Gennari[1], Paolo Visca[2], Federico Pierconti[3], Cecilia Coccia[3], Federico Cappuzzo[4], Isabella Sperduti[5], Francesco Facciolo[1] and Enrico Melis[1]

[1]Thoracic Surgery Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy, [2]Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy, [3]Anesthesiology and Intensive Care Unit, IRCCS- Regina Elena National Cancer Institute, Rome, Italy, [4]Medical Oncology 2, IRCCS Regina Elena National Cancer Institute, Rome, Italy, [5]Biostatistics, IRCCS Regina Elena National Cancer Institute, Rome, Italy

Introduction: Minimally invasive surgery has become the standard for the early-stage non-small cell lung cancer (NSCLC). The appropriateness of the kind of lung resection for the elderly patients is still debated.

Methods: We retrospectively reviewed patients with older than 75 years who underwent robotic lobectomy between May 2016 to June 2022. We selected 103 patients who met the inclusion criteria of the study. The preoperative cardiorespiratory functional evaluations were collected, and the risk of postoperative complications was calculated according to the Charlson Comorbidity Index, the American College of Surgery surgical risk calculator (ACS-NSQIP), EVAD score, and American Society of Anesthesiology (ASA) score. The patients were divided in two groups according to the presence of postoperative complications.

Results: Forty-three patients were female, and 72.8% of the total population were former or active smokers. Thirty-five patients reported postoperative complications. The analysis of the two groups showed that the predicted postoperative forced expiratory volumes in the first second (FEV1) and forced vital capacity (FVC) were significantly lower in patients presenting postoperative complications ($p=0.04$). Moreover, the upstaging rate and the unexpected nodal metastases were higher in the postoperative complication groups.

Conclusion: Robotic-assisted lobectomy for early-stage lung cancer is a safe and feasible approach in selected elderly patients. The factors that could predict the complication rate was the predicted postoperative FEV1 and the nodal disease.

KEYWORDS
NSCLC, rats, mediastinal lymphadenectomy, elderly, postoperative complications

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. The radical treatment of early-stage non-small cell lung cancer (NSCLC) is lobectomy and hilum-mediastinal lymphadenectomy (1, 2).

However, along with the improvement in life expectancy, the incidence rate of lung cancer has gradually increased among the elderly. Therefore, a growing number of patients present at diagnosis in their old age, with the pick in incidence at 75 years old (3–5). Moreover, the prevalence of frailty in NSCLC is 45% with a significant impact on survival (6).

In these patients, the new diagnosis of lung cancer is added to a significant burden of smoking-related comorbidities and chronic diseases, which impair functional reserve and may lay the ground for postoperative complications (7). To minimize the perioperative risk of complications, radical treatment is often sacrificed to reduce surgical trauma regardless of the risk of undertreatment and of a poor oncological outcome (8, 9).

In the last decades, minimally invasive surgery became the strategy of choice in the management of early-stage lung cancer, improving perioperative outcomes when compared to open surgery especially in the elderly, thus challenging the surgeon to extend radical surgery to these patients (10, 11).

In the context of minimally invasive surgery, robotic surgery is outgrowing thanks to its ability to enhance surgical maneuverability and visualization (12). Nonetheless, robotic surgery is demonstrated to improve oncological outcomes with a complication and conversion rate comparable to video-assisted surgery (13). However, the perioperative results of robotic-assisted lobectomy for early-stage lung cancer in patients older than 75 years have not been clearly assessed, and the best treatment strategy for NSCLC affecting the elderly is often omitted from guidelines and clinical trials leading to management ambiguities (9).

In order to evaluate the feasibility and the perioperative outcome of robotic lobectomy in patients with age higher than 75 years, we retrospectively analyzed our database of patients undergoing robotic pulmonary lobectomy at our institution. Clinical and pathological features affecting perioperative outcomes have been also analyzed.

Materials and methods

In this single-center retrospective analysis, patients older than 75 years underwent robotic lobectomy for NSCLC. Data for analysis were retrieved from our lobectomy database including patients operated on from May 2016 to June 2022. Moreover, clinical charts, surgical reports, and outpatient's clinic reports were reviewed to retrieve data about perioperative clinical and pathological characteristics and postoperative complications. General inclusion criteria for this study were patients diagnosed with NSCLC at clinical stage I and II undergoing robotic lobectomy. Patients with clinical stage III–IV were excluded; sublobar and wedge resections were also excluded.

Preoperative assessment

In all the patients, preoperative staging was achieved through total body computed tomography (CT) and F18-fluorodeoxyglucose positron emission tomography (FDG-PET). Bone scintigraphy was performed if clinically indicated. Patients presenting with suspected hilar or mediastinal nodal metastases underwent non-invasive eco-endoscopic biopsy. To evaluate resectability and to assess preoperative cardiopulmonary function, all the patients underwent spirometry, diffusion capacity of the lung for carbon monoxide (DLCO), and arterial blood gas analysis. Postoperative predicted (ppo) forced expiratory volumes in the first second (FEV1), forced vital capacity (FVC), and DLCO values were calculated according to the anatomical techniques (14). Further or more complex functional evaluations, including 6-min walking test and cardiac stress tests, were performed in patients presenting with impaired cardiopulmonary status (14). The performance status of each patient was calculated according to the Easter Cooperative Oncology Group (ECOG) performance status scale (15). Overall risk of postoperative complication was calculated according to Charlson Comorbidity Index (16), the American College of Surgery surgical risk calculator (ACS-NSQIP), EVAD score (17), and American Society of Anesthesiology (ASA) score (18). Frailty of the enrolled patients was considered according to the modified Frailty Index (19). Before the operations, all patients had signed an informed consent to lobectomy. All patients who underwent robotic-assisted thoracoscopic surgery (RATS) operations were alerted about the possibility of conversion to thoracotomy in case of unexpected technical problems. Before the operations, all patients had a discussion in the context of a multidisciplinary meeting with the thoracic surgeon, oncologist, radiotherapist, and pneumologist.

Surgical technique

All the patients underwent curative intended surgery by robotic-assisted lobectomy (using the Si da Vinci robot and the Xi da Vinci robot). Patients were placed in the lateral decubitus position using the single-lung ventilation with the hips fixed at the level of the table break and flexed to achieve maximum separation of the intercostal spaces. The Si da Vinci robot is positioned at the head of the patient. The Xi da Vinci robot is positioned at the back of the patient. We always proceeded performing a 3-cm utility incision at the fifth or sixth intercostal space anteriorly of the latissimus dorsi. The wound is usually protected with a soft tissue retractor. Then, we performed the other three operative ports under direct view guidance usually at the eighth or ninth intercostal space. We then started docking the robot. We always used a 30° stereoscopic robotic camera. Under direct view, the bed assistant started introducing the operative robotics arms. The lobectomy was carried out with the usual technique. The pulmonary vein, pulmonary artery, and lobar bronchus were individually isolated and divided with a vascular three-line stapler. A parenchymal stapler was also used for the division of incomplete fissures. The lobe was retrieved with an endoscopic bag. In the clinically negative-node octogenarian patients, systematic mediastinal lymphadenectomy was performed according to preoperative comorbidities, therapeutic chances, and surgical characteristics in order to avoid major complications and reduce operative time. A hilum-mediastinal lymph nodes sampling was carried out in all patients. At the end of the procedure, we usually inserted one chest tube using the camera port.

Postoperative evaluation and follow-up

The standardize postoperative management consisted of laboratory test and chest X-ray performed at postoperative days 1 and 5 or after removing chest drain. Pleural effusion and air leakages were recorded daily and recorded in the clinical chart for each patient. Chest drainages were considered for removal when no air leakages could be detected and the pleural effusion output was <150 ml/day. Air leakages were considered prolonged when lasting more than 5 days (20). Patients presenting prolonged air leakages could be discharged with chest drainage connected to a Heimlich valve according to the patient's preference and familiar context. Pleural effusion was considered persistent after 5 days of drainage output higher than 250 ml/day or when the drainage output was the only reason to prolong the patient in-hospital stay (21). Outpatient follow-up was performed by thoracic surgeons after 1 month from the operation. Standard follow-up consisted of chest X-ray, laboratory testing, and clinical examination. Postoperative complications were classified according to the Clavien–Dindo classification (22).

Objectives of the study

The primary objective of the study was to report and analyze the feasibility and the complications of robotic thoracoscopic lobectomy for clinical early-stage lung cancer in a selected population of elderly patients (age ≥75 years). The secondary objective was to compare patients undergoing postoperative complications with patients presenting a regular postoperative process. The main perioperative factors that can help to predict complications in this highly selected at-high risk population have been analyzed.

Statistical analysis

Statistical analysis was performed with SPSS 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Descriptive statistics was calculated and expressed as median and interquartile range (IQR).

Patients were divided in chronological order since the beginning of the thoracic robotic program in 2016 in three classes of 25 patients each and a fourth class composed of 28 patients. Postoperative complications rate has been compared among the fourth classes using χ^2 test to determine the role of operator proficiency in the postoperative complications rate.

Intergroup analysis was performed comparing patients undergoing postoperative complications versus patients undergoing a regular clinical progress to analyses perioperative factors that may influence postoperative complications rate. The distribution of perioperative characteristics of patients in each study group was compared by using analysis of variance for continuous variables and Fisher exact test or χ^2 test for categorical variables. Perioperative characteristics presenting statistically significant differences between the two groups (p-value < 0.05 was considered to be statistically significant) were included in the binary logistic regression model.

Results

Out of the 954 robotic procedures performed since the beginning of the thoracic robotic program at our institution, 103 elderly patients undergoing robotic lobectomy for clinical early-stage lung cancer with an age of more than 75 years old selected. Demographic and perioperative characteristics of the enrolled population are presented in Table 1. A fifth of the patients were older than 80 years at surgery, and up to 70% of the patients were active or former smokers. Of the patients with previous oncological history, 32% had breast cancer, 19% had gastrointestinal cancer, and 16% had urological cancer; other previous cancers were lymphoma, laryngeal cancer, endometrial cancer, and melanoma. None of the patients had previous pulmonary resections, and one patient had thoracic radiotherapy but presented at surgery with preserved respiratory function and did not experience postoperative complications. Comprehensively, 65% of the patients enrolled presented at surgery with solitary pulmonary nodules, while the other patients had pulmonary masses larger than 30 mm. Considering pulmonary functional evaluation, spirometry and DLCO data could be retrieved for 93 patients. Ten patients had permanent tracheostomy due to previous laryngeal surgery; thus, in these patients, spirometry and DLCO were not performed. Patients presenting with ppoFEV1 or ppoDLCO below 60% were 16 and 39, respectively, and 13 patients presented with both ppoFEV1 and ppoDLCO below 60%. In

TABLE 1 Demographic and perioperative characteristics of the enrolled population.

	Total (103)	Complication (35)	Regular progress (68)	p-value
Age, median (IQR) (years)	77 (76-79)	77 (76-79)	78 (76 - 79.3)	0.31
Female sex, n (%)	43 (41.7)	14 (40)	29 (42.6)	0.84
BMI (kg/m^2)	26.6 (24.4 - 29)	26.6 (24.7 -28.2)	26.7 (24.3 - 29.7)	0.685
Smoking habit, n (%)	75 (72.8)	27 (77.1)	48 (70.6)	0.79
Previous cancer, n (%)	62 (60.2)	23 (65.7)	39 (57.3)	0.52
Tumor diameter (mm)	28 (18 - 35.3)	30 (19.5 - 37.5)	25 (16.3 - 35)	0.385
Diameter > 30 mm, n (%)	38 (36.9)	14 (40)	24 (35.3)	0.67
Radiological aspect, n (%)				0.74
Solid	79 (76.7)	28 (80)	51 (75)	
Sub solid	12 (11.7)	3 (8.6)	9 (13.3)	
GGO	8 (7.8)	2 (5.7)	6 (8.8)	
Cavitary	4 (3.8)	2 (5.7)	2 (2.9)	
Central type	18 (17.5)	8 (22.9)	10 (14.7)	0.41
Clinical stage				0.5
IA	39 (37.9)	14 (40)	25 (36.8)	
IB	37 (35.8)	11 (31.4)	26 (38.2)	
IIA	12 (11.7)	6 (17.2)	6 (8.8)	
IIB	15 (14.6)	4 (11.4)	11 (16.2)	
FEV1 (L/min)	2.1 (1.7 - 2.5)	2 (1.6 - 2.4)	2.2 (1.8- 2.6)	0.301
%FEV1	100 (86 - 121.3)	104.5 (86 - 123.8)	93 (84 - 104)	0.192
FVC (l)	2.8 (2.2 - 3.4)	2.5 (2.3 - 3.3)	2.8 (2.2 - 3.5)	0.566
%FVC	101.5 (93 - 122.5)	100 (89 - 116)	102 (93 - 124.5)	0.236
DLCO	15.9 (13.8 -19.4)	16.5 (13.7 - 19.7)	15.8 (13.8 - 19.1)	0.581
%DLCO	78 (67 - 92)	79 (66- 90)	78 (67.8 - 92)	0.936
%ppoFEV1	78.9 (65.5 - 94)	72.2 (64.1 - 89.2)	82.9 (67.8 - 98.1)	0.043
%ppoFEV1 < 60%	16 (15.5)	8 (22.9)	8 (11.8)	0.16
%ppoFVC	80.5 (72 - 92.6)	75.9 (66.3 - 88.4)	83.3 (74.8 - 96.5)	0.046
%ppoFVC < 60%	6 (5.8)	3 (8.6)	3 (4.4)	0.41
%ppoDLCO	63.2 (53.4 - 72)	59.7 (50.7 - 70.7)	65.2 (53.7 - 71.8)	0.449
%ppoDLCO < 60%	39 (37.9)	17 (48.6)	22 (32.4)	0.13
Upper lobectomy	53 (51.5)	19 (54.3)	34 (50)	0.84
Operative time (min)	229 (194 - 277.5)	240 (192 - 297.5)	194.5 (222.5 - 266.3)	0.517
Lymphadenectomy, n (%)				0.37
Systematic	32 (31.1)	14 (40)	18 (26.5)	
Lobar specific	36 (35)	11 (31.4)	25 (36.8)	
None	35 (33.9)	10 (28.6)	25 (36.8)	
Histology, n (%)				0.12
Adenocarcinoma	83 (80.6)	25 (71.4)	58 (85.3)	
Squamous cell carcinoma	20 (19.4)	10 (28.6)	10 (14.7)	
pathologic stage, n (%)				0.26
IA	34 (33)	10 (28.6)	24 (35.3)	
IB	35 (33.9)	12(34.3)	23 (33.8)	
IIA	11 (10.7)	3 (8.6)	8 (11.8)	
IIB	18 (17.5)	6 (17.1)	12 (17.6)	
IIIA	5 (4.9)	4 (11.4)	1 (1.5)	
In-hospital stay (days)	7 (5 - 8.3)	7 (5 - 8.4)	7 (5 - 8)	0.091

BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 min; FVC, forced vital capacity; ppo, predicted postoperative.

these patients, 6-min walking test was performed with satisfying results. Nearly half of the patients were ASA III, and 80% of the patients presented an ACS NSQIP risk above average. The results of CCI, EVAD score, and of the other risk stratification tools are presented in Table 2.

The most frequent surgical procedure performed was left upper lobectomy. No intraoperative complications were recorded. At pathological examination, 80% of the patients had adenocarcinoma, and radical resection was achieved in all the enrolled patients. Nodal assessment, either through radical lymphadenectomy or lobo-specific lymphadenectomy, was performed in 52 patients. Unexpected hilar nodal metastases were found in nine patients, while two patients had metastases in both hilar and mediastinal lymph nodes. Upstaging due to postoperative minor complications were recorded in 31 patients. Major complications were recorded in four patients. Two required re-operation due to middle lobe torsion and postoperative hemothorax, respectively. One patient developed postoperative chronic respiratory failure requiring at-home oxygen administration, and one developed postoperative pleural effusion requiring thoracentesis in the outpatient clinic (Figure 1). No 30 days mortality was observed, and all the patients were in good clinical conditions at the 1-month reassessment.

As proficiency in robotic surgery has a major impact on robotic lobectomy perioperative outcome (23), patients have been stratified in chronological order since the beginning of the thoracic robotic program in three groups of 25 patients each and a fourth group of 28 patients. As shown in Figure 2, patients in the first two groups, operated at the beginning of the robotic thoracic program, had a 42% complications rate, while complications rate in the last two groups, including patients operated later in thoracic robotic program, dropped to 26.4%. Despite the progressive reduction in complications rate, complications distribution in the four groups failed to achieve a statistically significant difference (p=0.4).

Perioperative characteristics of the patients undergoing postoperative complications or regular postoperative progress have been compared. As showed in Figure 3, at intergroup analysis, ppoFEV1 and ppoFVC demonstrated to be significantly lower in patients presenting postoperative complications (p=0.04; p=0.04). Moreover, patients in the complications group had a higher rate of pathological upstaging (p=0.006) and a higher rate of unexpected nodal metastases (p=0.04).

TABLE 2 Risk stratification based on multiple scores.

	Total (103)	Complication (35)	Regular progress (68)	p-value
ASA, n (%)				0.84
2	55 (53.4)	18 (51.4)	37 (54.4)	
3	48 (46.6)	17 (48.6)	31 (45.6)	
ACS-NSQIP				
Any complications	14,6 (12.1 - 19.8)	14.6 (10.5 - 19.6)	14.7 (12.5 - 19.8)	
Any complications > 9.6%	83 (80.6)	28 (80)	55 (80.9)	0.88
Serious complications	13.9 (10.4 - 18.2)	13.6 (9.4 - 17.7)	13.9 (10.6 - 18.6)	
Serious complications > 8.3%	87 (84.5)	29 (82.9)	58 (85.3)	0.78
Charlson Comorbidity Index, n(%)				0.81
5	27	11	16	
6	29	10	19	
7	21	6	15	
≥8	26	8	18	
Modified Frailty Index, n (%)				0.39
1	27	8	19	
2	31	13	18	
3	19	8	11	
≥4	26	6	20	
EVAD score				0.48
3-4	33	14	19	
5-6	29	9	20	
7-8	19	7	12	
≥9	22	5	17	
TcRCRI	3	1	2	1

ASA, American Society of Anesthesia; TcRCRI, Revised Cardiac Risk Index.

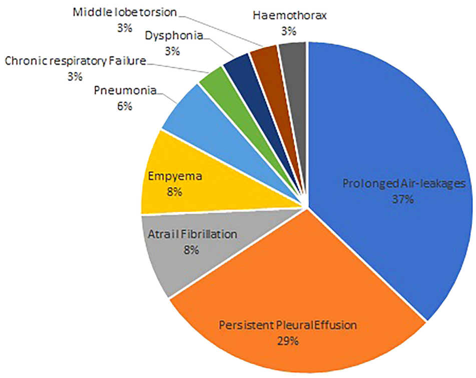


FIGURE 1
Distribution of the different postoperative complications.

These results remain statistically significant when only patients undergoing radical or lobar-specific lymphadenectomy have been included in the analysis. In this selected population, 10 out 25 patients undergoing postoperative complications pathological upstaging compared to 6 out 43 in the regular postoperative progress group (p=0.01) and 6 out 25 versus 2 out 43 had unexpected nodal metastases in the same groups (p=0.04). In our analysis, upstaging was mainly related to unexpected hilar or mediastinal nodal involvement determining the upstage to IIB or IIIA (locally advanced stage). In nine patients, unexpected visceral pleural invasion of peripheral nodules or radiologically undetected additional nodules in the same lobe of the primary lesion were the pathological upstaging determinant. As a consequence, the complications group had a higher rate of IIIA pathological stage when compared to the patients presenting a regular postoperative progress (p=0.04). However, no differences in the rates of systematic or lobar-specific lymphadenectomy could be found in the two groups (p=0.36). Among the analyzed perioperative characteristics, ppoFEV1, ppoFVC, pathological upstaging, and unexpected nodal metastases have been included in the binary logistic regression model (Table 2). Pathological upstaging was the only parameter able to predict postoperative complications (OR, 0.123; 95% CI, 0.21–0.720; p=0.02). Finally, no differences could be found in age, sex, clinical stage, tumoral diameter, NSQIP score, EVAD score, ASA score, modified Frailty Index, CCI, FEV1, FVC, DLCO, PaO2, ppoDLCO, operative time, histology, and in-hospital stay.

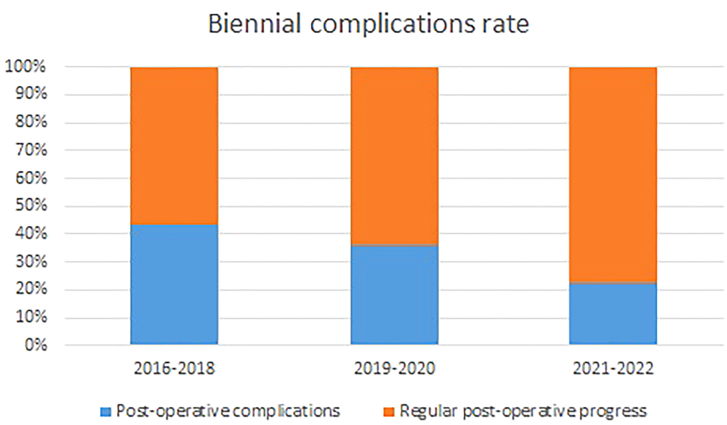


FIGURE 2
Distribution of the postoperative complications according the biennium.

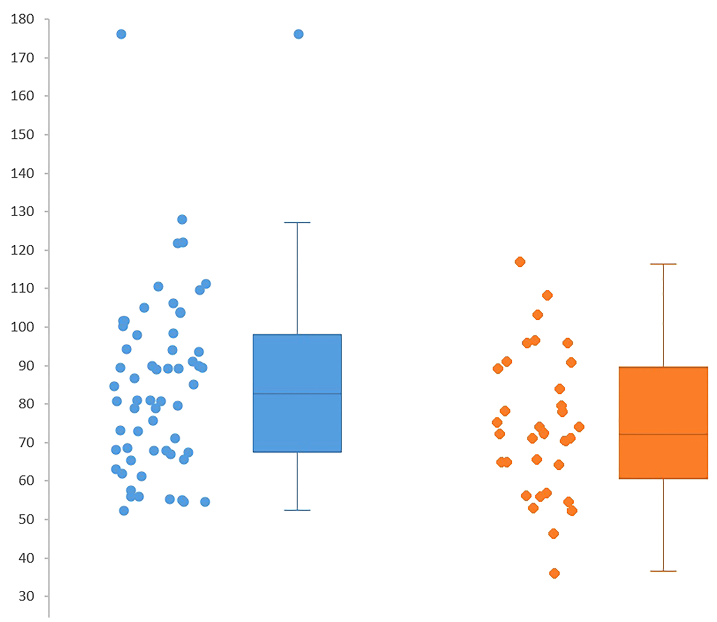


FIGURE 3
ppoFEV1 and ppoFVC evaluations in complications group vs complication group.

Discussion

In this single-institution retrospective analysis, the perioperative outcomes of robotic pulmonary lobectomy for clinical early-stage lung cancer in patients older than 75 years were evaluated. Robotic resection could be accomplished in all the patients. Of the 103 patients, 35 patients developed postoperative complications. Minor complications were observed in 31 patients, requiring in-hospital prolongation or adjunctive pharmacological treatment, while four patients had major complications including two patients that underwent reoperation due to postoperative hemothorax and middle lobe torsion, respectively, one patient that required postoperative thoracentesis, and one patient that required at-home oxygen administration. In 65.7% of the instances, postoperative complications were prolonged air leakages and persistent pleural effusions. Both prolonged air leakage and persistent pleural effusion were treated conservatively. Pleuropulmonary infectious complications were followed with 17.1% of the complications including three patients presenting with postoperative pneumonia and three patients presenting with postoperative empyema. These patients were discharged with clinical and radiological resolution of the infection after antibiotic treatment. In patients presenting complications requiring surgical re-intervention or thoracentesis, the postoperative progress after the second surgical procedure was uneventful.

Surgical management of the elderly presenting with early-stage NSCLC has been questioned, especially as both age at diagnosis and treatment choices have radically increased through the last decades (8). The absence of univocal guidance in older patients lead to a 10% rate of undertreated elderly patients that would have benefited from an active treatment (9). In early-stage lung cancer, curative intended surgery was limited to nearly half of the patients aged 65–75 years, and the percentage further decreased in older patients (24).

Minimally invasive thoracic surgery, particularly robotic surgery, is thought to reduce surgical stress and postoperative complications still pursuing a radical intended pulmonary resection (12, 25). In the elderly, robotic pulmonary lobectomy complications rate was demonstrated to be lower than that in open surgery but similar to that in video-assisted thoracic surgery with an overall incidence approximately 30% (10, 11). These results are consistent with our findings demonstrating an overall complications rate of 33.9%. Moreover, as proficiency in robotic surgery is associated with a 15% relative reduction in 30-day overall postoperative complications (23), we evaluated the complications rate of the patients operated on in the last period of our robotic thoracic program, achieving a 25% complications rate.

Regardless of the surgeons' proficiency, further stratification tolls may help to further reduce perioperative risk in these patients. For this reason, preoperative scores or functional test able to predict complications has been an area of interest in order to reduce surgical-related risk in patients undergoing major pulmonary resections with pre-existing impaired cardiopulmonary function or borderline age (14). Since 1973, FEV1 was identified to be a predictor of pulmonary resection tolerability, and spirometry became the standard in the evaluation of candidates for lung resection (26). Subsequently, it became evident that postoperative pulmonary function may be affected by the extension of surgical resection, and absolute preoperative FEV1 rapidly gave way to ppoFEV1 as a predictor of postoperative pulmonary complications. In this report, ppoFEV1 and ppoFVC distributions were demonstrated to be significantly lower in the postoperative complications group when compared to the regular postoperative progress group. Conversely, no differences could be found in the distributions of preoperative FEV1, FVC, or DLCO. The reduced reliability of preoperative spirometric values in minimally invasive approaches had been previously demonstrated in a retrospective analysis comparing video-assisted thoracic surgery and open thoracotomy (27). In contrast, ppoFEV1 correctly predicted postoperative complication after major pulmonary resection regardless of the surgical approach (28). According to the American College of Chest Physician guidelines, patients with ppoFEV1<60% should be referred for further cardiopulmonary function test (14). However, in our analysis, there were no differences between the two groups in the rate of patients under the ppoFEV1 <60% cutoff. As shown in Figure 3, according to the distributions of ppoFEV percentage values in the two groups, in this high-risk population, a more conservative cutoff at ppoFEV1 <80% may help to direct patients older than 75 years for further examinations such as cardiopulmonary exercise test or low-tech exercise test.

In the current study, both upstaging and unexpected hilar and mediastinal nodal metastases rates were higher in the postoperative complications group. Moreover, at binary logistic regression, upstaging was the only predictor of postoperative complications. Reasons underneath these results are debatable. The higher overall and nodal upstaging rates may be the results of a higher rate of lymphadenectomy that would subsequently explain the association with postoperative complications. However, no differences could be retrieved between the two groups in systematic, lobar-specific lymphadenectomy or sampling. As a reasonable explanation, pathological diagnosis of previously undetectable additional nodules, pleural infiltration, or nodal metastases may denote a more aggressive biological behavior of the disease. Therefore, the higher tumoral burden and the neoplastic lymphatic infiltration may impair pulmonary healing processes. Tumoral lymphatic invasion enhances inflammatory response, increasing microvascular permeability and eliciting pleural effusion (29). Nonetheless, malignant invasion of the thoracic lymphatic chain has been associated with the presence of substantial pleural effusion (30). Moreover, tumoral metastatic pathways have been associated with collagen deposition and pulmonary interstitial stiffness that may entail pulmonary re-expansion and enhance prolonged air leakages (31). Even if the reasons underlying the ability of upstaging and nodal upstaging in postoperative prediction may be unknown, the elderly may benefit from a more accurate hilar and mediastinal preoperative staging. On the basis of the increased complications risk, preoperative finding of pathological nodal metastases may help tailoring the best treatment strategy in this high-risk population. Nonetheless, preoperative molecular characterization may help to identify biological aggressive diseases that may benefit from a multimodal therapy.

This study has some limitations: the number of enrolled patients is limited due to the highly selective inclusion criteria; however, the application of non-parametric test in the statistical analysis may overcome this limit. Moreover, our findings demonstrated to be in trend with previous analyses presenting a similar study design in video-assisted thoracic surgery. Second, in the text, a progressive reduction in postoperative complications over time is shown. This can mostly result from an improvement in the robotic technique operators' proficiency. This progressive improvement in patients' perioperative outcome may have mitigated the effects of the parameters analyzed in the paper. However, when the comparison of complications rate in the stratified groups has been performed, no significant differences were retrieved, and since the beginning of our thoracic robotic program in 2016, the inclusion criteria for robotic lobectomy were consistent with no significant variations neither in the oncological nor in the functional assessment. Finally, due to the retrospective nature of the report, specific frailty evaluations or geriatric tools, other than the modified Frailty Index, to stratify high-risk patients could not be included in the analysis. Further studies are necessary to evaluate the benefits of specific frailty evaluations or geriatric tools as complementary exams to a strict pulmonary function evaluation, including predicted postoperative values and a more accurate preoperative staging.

Conclusion

Robotic-assisted lobectomy for early-stage lung cancer was demonstrated to be a safe and feasible treatment strategy in elderly patients. The analysis of the factors that can predict the complication rate in this specific surgical populations showed that the predicted postoperative FEV1 and the preoperative staging have to be carefully evaluated to help reduce postoperative complications. In the literature, there are no specific guidelines for the preoperative staging in the elderly population. Our results showed that the nodal disease could have an impact on the postoperative complications regardless of the kind of lymphadenectomy performed. Further studies should be done to understand how the elderly patients must be stratified preoperatively, but we believe that the risk of nodal metastasis could be considered equally to the comorbidities.

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 the IRCCS Regina Elena National Cancer Institute; Approval Code: 1465/21 Approval Date: 23 February 2021. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, FG, FF. Methodology, FG, EM, RT. Software, DF, RT. Validation, FF, FC, FP. Formal analysis, FG, RT, FC. Investigation, FC, PV. Resources, FF, EM, FC. Data curation, FG, RT. Writing—original draft preparation, FG, RT, EM, FF. Writing—review and editing, EM, FF, FC, DF. Visualization, CC, FP. Supervision, FF, EM. Project administration, CC, FF. Funding acquisition, FF. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to extend our deepest gratitude to the dedicated contributors over the years to our project. The authors want to thank the Scientific Direction of the IRCCS “Regina Elena” National Cancer Institute for the support to our work.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* (2015) 65:5–29. doi: 10.3322/caac.21254

2. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* (2013) 143 (Suppl. S5):e211S–50S. doi: 10.1378/chest.12-2355

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660

4. Venuta F, Diso D, Onorati I, Anile M, Mantovani S, Rendina EA. Lung cancer in elderly patients. *J Thorac Dis* (2016) 8(Suppl 11):S908–14. doi: 10.21037/jtd.2016.05.20

5. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. *Transl Lung Cancer Res* (2018) 7(3):220–33. doi: 10.21037/tlcr.2018.05.06

6. Komici K, Bencivenga L, Navani N, D'Agnano V, Guerra G, Bianco A, et al. Frailty in patients with lung cancer: A systematic review and meta-analysis. *Chest* (2022) 162(2):485–97. doi: 10.1016/j.chest.2022.02.027

7. Whitson BA, Groth SS, Duval SJ, Swanson SJ, Maddaus MA. Surgery for early-stage non-small cell lung cancer: A systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg* (2008) 86(6):2008–16. doi: 10.1016/j.athoracsur.2008.07.009

8. Bertolaccini L, Viti A, Terzi A. "Old people suffer the ravages of the years": Changes of treatments in elderly patients with early stage non-small cell lung cancer. *Ann Transl Med* (2015) 3(9):114. doi: 10.3978/j.issn.2305-5839.2015.06.02

9. Lindqvist J, Jekunen A, Sihvo E, Johansson M, Andersén H. Effect of adherence to treatment guidelines on overall survival in elderly non-small-cell lung cancer patients. *Lung Cancer* (2022) 171:9–17. doi: 10.1016/j.lungcan.2022.07.006

10. Chen DL, Kang PM, Tao SL, Wu LC, Li QY, Tan Q. Comparative short-term outcomes of robotic-assisted surgery for older patients with non-small cell lung cancer: A propensity matched study. *Updates Surg* (2022) 74(3):1087–96. doi: 10.1007/s13304-021-00992-x

11. Veluswamy RR, Whittaker Brown SA, Mhango G, Sigel K, Nicastri DG, Smith CB, et al. Comparative effectiveness of robotic-assisted surgery for resectable lung cancer in older patients. *Chest* (2020) 157(5):1313–21. doi: 10.1016/j.chest.2019.09.017

12. Gallina FT, Tajè R, Forcella D, Corzani F, Cerasoli V, Visca P, et al. Oncological outcomes of robotic lobectomy and radical lymphadenectomy for early-stage non-small cell lung cancer. *J Clin Med* (2022) 11(8):2173. doi: 10.3390/jcm11082173

13. Gallina FT, Melis E, Forcella D, Mercadante E, Marinelli D, Ceddia S, et al. Nodal upstaging evaluation after robotic-assisted lobectomy for early-stage non-small cell lung cancer compared to video-assisted thoracic surgery and thoracotomy: A retrospective single center analysis. *Front Surg* (2021) 8:666158. doi: 10.3389/fsurg.2021.666158

14. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* (2013) 143(5 Suppl):e166S–90S. doi: 10.1378/chest.12-2395

15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern cooperative oncology group. *Am J Clin Oncol* (1982) 5(6):649–55. doi: 10.1097/00000421-198212000-00014

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* (1987) 40(5):373–83. doi: 10.1016/0021-9681(87)90171-8

17. Ferguson MK, Durkin AE. A comparison of three scoring systems for predicting complications after major lung resection. *Eur J Cardiothorac Surg* (2003) 23(1):35–42. doi: 10.1016/S1010-7940(02)00675-9

18. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* (1941) 2:281–4. doi: 10.1097/00000542-194105000-00004

19. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-factor modified frailty index using American college of surgeons NSQIP data. *J Am Coll Surg* (2018) 226(2):173–81. doi: 10.1016/j.jamcollsurg.2017.11.005

20. Brunelli A, Cassivi SD, Halgren L. Risk factors for prolonged air leak after pulmonary resection. *Thorac Surg Clin* (2010) 20(3):359–64. doi: 10.1016/j.thorsurg.2010.03.002

21. Cerfolio RJ, Bryant AS. Results of a prospective algorithm to remove chest tubes after pulmonary resection with high output. *J Thorac Cardiovasc Surg* (2008) 135(2):269–73. doi: 10.1016/j.jtcvs.2007.08.066

22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae

23. Reddy RM, Gorrepati ML, Oh DS, Mehendale S, Reed MF. Robotic-assisted versus thoracoscopic lobectomy outcomes from high-volume thoracic surgeons. *Ann Thorac Surg* (2018) 106(3):902–8. doi: 10.1016/j.athoracsur.2018.03.048

24. Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. *J Clin Oncol* (2012) 30(13):1447–55. doi: 10.1200/JCO.2011.39.5269

25. Nelson DB, Mehran RJ, Mitchell KG, Rajaram R, Correa AM, Bassett RLJr, et al. Robotic-assisted lobectomy for non-small cell lung cancer: A comprehensive institutional experience. *Ann Thorac Surg* (2019) 108(2):370–6. doi: 10.1016/j.athoracsur.2019.03.051

26. Lockwood P. Lung function test results and the risk of post-thoracotomy complications. *Respiration* (1973) 30(6):529–42. doi: 10.1159/000193062

27. Brunelli A, Monteverde M, Salati M, Borri A, Al Refai M, Fianchini A. Stair-climbing test to evaluate maximum aerobic capacity early after lung resection. *Ann Thorac Surg* (2001) 72(5):1705–10. doi: 10.1016/S0003-4975(01)03100-9

28. Epstein SK, Faling LJ, Daly BD, Celli BR. Predicting complications after pulmonary resection. preoperative exercise testing vs a multifactorial cardiopulmonary risk index. *Chest* (1993) 104(3):694–700. doi: 10.1378/chest.104.3.694

29. Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J Mol Med (Berl)* (1999) 77(7):527–43. doi: 10.1007/s001099900019

30. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. *Am J Med* (1977) 63(5):695–702. doi: 10.1016/0002-9343(77)90154-1

31. Navab R, Strumpf D, To C, Pasko E, Kim KS, Park CJ, et al. Integrin α11β1 regulates cancer stromal stiffness and promotes tumorigenicity and metastasis in non-small cell lung cancer. *Oncogene* (2016) 35(15):1899–908. doi: 10.1038/onc.2015.254

TYPE Original Research
PUBLISHED 30 November 2022
DOI 10.3389/fonc.2022.1032443

OPEN ACCESS

EDITED BY
Felix Berlth,
Johannes Gutenberg University Mainz,
Germany

REVIEWED BY
Gianni Mura,
Ospedale del Valdarno, Italy
Ugo Elmore,
San Raffaele Hospital (IRCCS), Italy

*CORRESPONDENCE
Daniel Reim
daniel.reim@tum.de;
www.chir.med.tum.de

SPECIALTY SECTION
This article was submitted to
Surgical Oncology,
a section of the journal
Frontiers in Oncology

RECEIVED 30 August 2022
ACCEPTED 31 October 2022
PUBLISHED 30 November 2022

CITATION
Berlet M, Weber M-C, Neumann P-A, Friess H and Reim D (2022) Gastrectomy for cancer beyond life expectancy. A comprehensive analysis of oncological gastric surgery in Germany between 2008 and 2018. *Front. Oncol.* 12:1032443. doi: 10.3389/fonc.2022.1032443

Gastrectomy for cancer beyond life expectancy. A comprehensive analysis of oncological gastric surgery in Germany between 2008 and 2018

Maximilian Berlet, Marie-Christin Weber, Philipp-Alexander Neumann, Helmut Friess and Daniel Reim*

Department of Surgery, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

Introduction: Major gastric surgery for distal esophageal and gastric cancer has a strong impact on the quality of life, morbidity, and mortality. Especially in elderly patients reaching their life expectancy, the responsible use and extent of gastrectomy are imperative to achieve a balance between harm and benefit. In the present study, the reimbursement database (German Diagnosis Related Groups (G-DRG) database) of the Statistical Office of the Federal Republic of Germany was queried to evaluate the morbidity and mortality of patients aged above or below 75 years following gastrectomy.

Material and methods: All patients in Germany undergoing subtotal gastrectomy (ST), total gastrectomy (T), or gastrectomy combined with esophagectomy (TE) for gastric or distal esophageal cancer (International Statistical Classification of Diseases and Related Health Problems Version 10 (ICD-10) C15.2, C15.5, and C16.0–C16.9) between 2008 and 2018 were included. Intraoperative and postoperative complications as well as comorbidities, in-hospital mortality, and the extent of surgery were assessed by evaluating ICD-10 and operation and procedure key (Operationen- und Prozedurenschlüssel) codes.

Results: A total of 67,389 patients underwent oncologic gastric resection in Germany between 2008 and 2018. In total, 21,794 patients received ST, 41,825 received T, and 3,466 received TE, respectively. In 304 cases, the combinations of these, in fact, mutually exclusive procedures were encoded. The proportion of patients aged 75 years or older was 51.4% (n = 11,207) for ST, 32.6% (n = 13,617) for T, and 28.1% (n = 973) for TE. The in-hospital mortality of elderly patients was significantly increased in all three groups. ($p < 0.0001$) General complications such as respiratory failure ($p = 0.0054$), acute renal failure ($p < 0.0001$), acute myocardial failure ($p < 0.0001$), and the need for resuscitation (ST/T: $p < 0.0001$/ TE: $p = 0.0218$) were significantly increased after any kind of gastrectomy. Roux-en Y was the most commonly applied reconstruction technique in both young and elderly patients. Regarding lymphadenectomy, systematic D2 dissection was performed less frequently in older patients than in the younger collective in the case of ST and T as well as D3 dissection. Peritonectomy and hyperthermic intraperitoneal chemotherapy were uncommon in elderly patients alongside ST and T compared to younger patients ($p < 0.0001$).

Conclusion: The clinical outcome of major oncological gastric surgery is highly dependent on a patient's age. The elderly show a tremendously increased likelihood of in-hospital mortality and morbidity.

KEYWORDS

elderly patients, gastrectomy, gastric cancer, esophageal cancer, clinical outcome, comorbidity, mortality

Introduction

Oncologic resection for gastric cancer by either partial or total gastrectomy is the main pillar of curative treatment aside from multimodal therapies in advanced stages, which may be a critical matter from numerous aspects. On one hand, an oncologically radical approach is important in order to achieve R0 resection (1), but, on the other hand, gastrectomy is correlated to a high mortality rate of up to 20% (2). In particular, age-related aspects regarding surgery for gastric cancer have not been adequately investigated yet. Thus, most studies only focus on surgical technique and cancer specifications and do not cover the entire collective of elderly patients requiring therapy for gastric cancer (3, 4). Articles related to elderly gastrectomy patients usually address the best surgical technique in terms of minimally invasive and robotic-assisted surgery (5–7). With regard to stratification by age, several aspects are of particular interest. For example, perioperative mortality and the probability of other postoperative complications must be weighed against current life expectancy without surgery (8). Recent study collectives are mostly small in number. In addition, the results being published may be biased due to the fact that these studies are mostly reporting on patient cohorts from specialized treatment centers not representing common clinical nationwide practice. Therefore, a systematic analysis of large case numbers is urgently needed to evaluate the influence of age on the surgical outcome related to major gastric surgery, especially when life expectancy is reached. The aim of the present study was to evaluate the clinical outcomes of patients aged beyond the average life expectancy undergoing surgery for gastric cancer in a population-based study using a structured query of the German Diagnosis Related Groups (G-DRG) database of the German Statistical Office (DESTATIS). The complete database is accessible only for selected researchers and contains all the diagnoses and medical procedures of inpatients treated in German hospitals, which were encoded according to the International Classification of Diseases version 10 with the German modification (ICD-10-GM) and the German operation and procedure key ('Operationen- und Prozedurenschlüssel', OPS) (9).

Material and methods

All patients with gastric and distal esophageal cancer (ICD C15.2, C15.5, and C16.0–C16.9) receiving major gastric surgery in terms of subtotal gastrectomy (ST, OPS 5-435, 5-436), total gastrectomy (T, OPS 5-437), and total gastrectomy with esophageal resection (TE, OPS 5-438) in Germany between 2008 and 2018 were included. The parameters queried comprised comorbidity, reconstruction technique, the extent of lymphadenectomy (LAD), adjunctive therapy and organ resection, intraoperative and postoperative adverse events, and perioperative mortality. These factors were then analyzed for age dependency by setting a cutoff at 75 years. Patients younger than this age were assigned to group L75 ('less than 75 years'), and older patients were assigned to group G75 ('greater or equal to 75 years'). Intraoperative and postoperative complications were defined according to the international consensus on complications after gastrectomy for cancer (10). The source code for the query of the G-DRG database was created in the SAS programming language, as required by DESTATIS (9). The same program code was executed separately for each year of interest. Diagnoses and complications were defined using the most appropriate ICD-10 and OPS codes available (see the supplement for details). Statistical analysis was then performed using R statistical software version 3.6 without additional packages (11). To calculate significance, the Wilcoxon rank sum test was used for the Charlson comorbidity scores and the chi-square test and Fisher's exact test were applied to nominal scaled parameters. In case of multiple testing, Bonferroni correction was used to adjust p-values. The particular statistical tests applied to the data and the absolute subgroup sizes are depicted in each table and figure. Relative frequencies are given for mortality, complications, the reconstruction technique, LAD, and adjunctive therapy. The Charlson index for comorbidity is reported as the mean and standard deviation for each collective and year. The significance level was set at 5%.

Results

A total of 67,389 patients with gastric or distal esophageal cancer underwent major gastric resection in Germany during the observation period (ST: 21,794/T: 41,825/TE: 3,466/ combinations of OPS codes for ST, T, or TE: 304 cases). The proportion of patients with an age of 75 years or more (G75) was 51.4% (n = 11,207) for ST, 32.6% (n = 13,617) for T, and 26.9% for TE (n = 973).

For the analysis of comorbidity, the Charlson comorbidity index in its classic version was calculated for both collectives (12). For each individual year and each type of gastric resection, there was a significantly higher score found in the elderly group (Table 1).

The pattern of reconstruction techniques, in terms of the use of Billroth II (BII), analog to Billroth II (aBII), Roux en Y-like (RY), or other (O) reconstruction, was almost the same in both age groups with slight differences regarding modified techniques. Nevertheless, the number of BII reconstructions was higher in elderly patients undergoing ST (30.7 vs. 26.2%). Following all gastric resection types, RY was the most frequently used technique in both groups (Figures 1A, B). Regarding LAD, systematic D2 LAD was the most frequently used procedure after total gastrectomy and gastrectomy combined with esophagectomy in patients <75 years and ≥75 years. D3 dissection was performed less commonly in the G75 collective (ST: 3.2 vs. 5.7%/T: 6.8 vs. 9.2%/TE: 7.9 vs. 11.6%) After subtotal resection, LAD strategies other than straight systematic D2 or D3 LAD were used in 51.4% (L75) and 62.1% (G75) including partly D2 or D3 dissection, respectively (Figures 1C, D).

While the type of reconstruction did not differ substantially between the two age groups, the extent of further therapy and additional organ resection appeared to be markedly divergent. Less aggressive approaches were observed for pancreatic resection after subtotal and total gastrectomy (ST: 1.3 vs. 2.3%, OR 0.58, $CI_{95\%}$ 0.46–0.71, $p < 0.0001$/T: 3.6 vs. 4.5%, OR 0.80, $CI_{95\%}$ 0.72–0.89, $p = 0.0005$). Partial or total adrenalectomy was less frequently performed in the G75 group alongside total gastrectomy (0.4 vs. 0.9%, OR 0.48, $CI_{95\%}$ 0.35–0.64, $p < 0.0001$). In contrast, there was no significant difference between the two groups in terms of splenectomy for subtotal and total gastrectomy or combined gastrectomy and esophagectomy. Most extensive methods, such as

TABLE 1 Charlson comorbidity score of patients undergoing major gastric surgery in Germany between 2008 and 2018.

Group		Parameter	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	p-value
<75	ST	Mean	**4.77**	**4.89**	**5.15**	**4.98**	**5.11**	**5.32**	**5.44**	**5.5**	**5.22**	**5.4**	**5.58**	
		sd	3.2	3.23	3.4	3.34	3.37	3.45	3.46	3.57	3.62	3.49	3.56	
		n	1,144	1,095	1,012	969	962	946	945	946	848	869	851	
	T	Mean	**4.77**	**4.9**	**5.17**	**5.13**	**5.2**	**5.46**	**5.49**	**5.64**	**5.56**	**5.79**	**5.64**	
		sd	3.32	3.34	3.45	3.45	3.44	3.53	3.51	3.57	3.5	3.54	3.48	
		n	2,887	2,774	2,661	2,598	2,475	2,395	2,843	2,701	2,382	2,314	2,178	< 0.0001
	TE	Mean	**4.5**	**5.41**	**4.94**	**5.38**	**5.23**	**5.86**	**5.74**	**6.17**	**5.73**	**6.05**	**5.88**	
		sd	3.27	3.41	3.3	3.16	3.56	3.71	3.41	3.59	3.45	3.56	3.51	
		n	140	179	135	148	150	152	214	194	403	406	372	
≥75	ST	Mean	**6.76**	**7.16**	**7.49**	**7.21**	**7.46**	**7.54**	**7.71**	**7.96**	**7.9**	**7.87**	**7.96**	
		sd	3.07	3.24	3.34	3.31	3.41	3.31	3.48	3.61	3.47	3.64	3.57	
		n	1,167	1,089	1,016	988	987	984	1,029	1,057	945	992	953	< 0.0001
	T	Mean	**6.89**	**6.99**	**7.39**	**7.37**	**7.44**	**7.79**	**7.86**	**7.79**	**8.12**	**7.97**	**8**	
		sd	3.26	3.22	3.43	3.42	3.4	3.52	3.56	3.51	3.62	3.55	3.57	
		n	1,205	1,208	1,108	1,197	1,208	1,237	1,380	1,385	1,297	1,228	1,164	< 0.0001
	TE	Mean	**7.44**	**6.81**	**7.21**	**7.24**	**8**	**7.88**	**7.14**	**7.82**	**7.88**	**8.25**	**8.47**	
		sd	3.21	3.38	3.11	3.37	3.6	3.48	3.1	4.1	3.61	3.53	3.67	
		n	57	54	56	54	48	59	71	79	164	173	158	

< 75: patients, younger than 75 years, ≥ 75: patients with an age of 75 years or older, ST, subtotal gastrectomy, T, total gastrectomy, TE, combined total gastrectomy and esophageal resection, mean, mean of the Charlson comorbidity index, sd, standard deviation of the Charlson comorbidity index, n, number of patients in the particular group; the Wilcoxon rank sum test with Bonferroni adjustment was used for statistical testing with a level of significance set at 5%. The difference between L75 and G75 was significant for each single year under study.
The bold values represent the mean values.

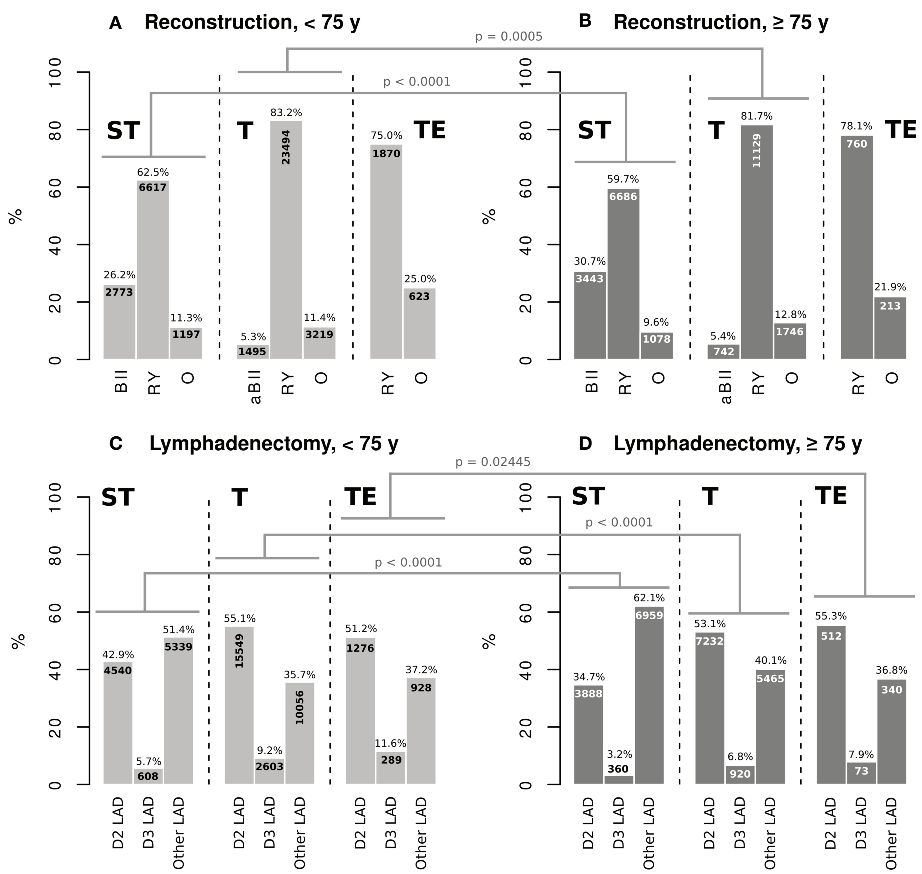


FIGURE 1
ST: subtotal gastrectomy, T: total gastrectomy, TE: gastrectomy combined with esophagectomy, BII: Billroth II reconstruction, aBII reconstruction analogue to Billroth II, RY: Roux en-Y reconstruction, O: other reconstruction technique, D2 LAD: straight D2 lymphadenectomy, D3 LAD: straight D3 lymphadenectomy, Other LAD: extent of lymphadenectomy other than straight systematic D2 or D3, Chi-square test with Bonferroni adjustment was applied for statistical testing. The significance level was set at 5%.

peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC), were used rarely in elderly patients in association with all three types of gastric surgery (Table 2).

General and surgical complications were subgrouped into intraoperative and postoperative adverse events according to the international consensus of complications after gastrectomy for cancer (10). The intraoperative course in terms of unintended injury to anatomic structures such as solid organs and blood vessels, during ST and T was slightly increased in elderly patients. (ST: 1.7 vs. 1.2%, OR 1.43, $CI_{95\%}$ 1.14–1.81, p = 0.0173/T: 2.2 vs. 1.7%, OR 1.28, $CI_{95\%}$ 1.10–1.48, p = 0.0109) Intraoperative bleeding and the need for interruption of surgery were not impacted by age (Table 3A).

Significant differences between the two groups, L75 and G75, were found in the postoperative course. General complications such as respiratory and acute renal failure, acute myocardial dysfunction, and the need for resuscitation were increased after subtotal and total gastrectomy in G75. In addition, elderly patients were significantly more susceptible to infections after all three types of gastric resection were studied (Table 3B).

Regarding specific surgical complications, the elderly had a significantly increased need for blood transfusions after each type of surgery. Furthermore, older patients showed an increased risk of bowel perforation (1.1 vs. 0.69%, OR 1.64, $CI_{95\%}$ 1.32–2.04, p < 0.0002) and anastomotic leakage (9.8 vs. 7.4%, OR 1.37, $CI_{95\%}$ 1.24–1.51, p < 0.0001) if they received total gastrectomy (Table 3C).

In-hospital mortality in elderly patients was higher after all three types of gastrectomy compared with the L75 group. (ST: 11.0 vs. 4.36%, OR 2.71, $CI_{95\%}$ 2.42–3.03, p < 0.0001/T: 11.9 vs. 4.23%, OR 3.05, $CI_{95\%}$ 2.82–3.30, p < 0.0001/TE: 13.9 vs. 5.86%, OR 2.59, $CI_{95\%}$ 1.99–3.35, p < 0.0001) (Table 4)

TABLE 2 Adjunctive therapy and organ resection alongside oncological gastric resection in elderly patients in Germany between 2008 and 2018.

Adjunctivetherapy	Subtotal gastrectomy (ST)						
	< 75 y		≥ 75 y				
	n	%	n	%	OR	$CI_{95\%}$	p-value
Pancreatic resection	**239** (10,587)	2.3%	**147** (11,207)	1.3%	0.58	0.46–0.71	**<0.0001**
Liver resection	**609** (10,587)	5.8%	**570** (11,207)	5.1%	0.88	0.78–1.00	0.6508
Splenectomy	**206** (10,587)	1.9%	**267** (11,207)	2.4%	1.23	1.00–1.49	0.6040
Peritonectomy	**108** (9,443)	1.1%	**23** (6,044)	0.4%	0.33	0.20–0.52	**<0.0001**
HIPEC	**58** (9,443)	1.1%	**0** (9,087)	0.0%	–	–	**<0.0001**
Colon resection	**398** (10,587)	3.8%	**434** (11,207)	3.9%	1.03	0.89–1.90	1.0000
Adrenalectomy	**21** (5,523)	0.38%	**16** (5,988)	0.27%	0.70	0.34–1.41	1.0000

Adjunctivetherapy	Total gastrectomy (T)						
	< 75 y		≥ 75 y				
	n	%	n	%	OR	$CI_{95\%}$	p-value
Pancreatic resection	**1,270** (28,208)	4.5%	**494** (13,617)	3.6%	0.80	0.72–0.89	**0.0005**
Liver resection	**1,791** (28,208)	6.3%	**771** (13,617)	5.7%	0.89	0.81–1.00	0.1282
Splenectomy	**2,898** (28,208)	10.3%	**1,412** (13,617)	10.4%	1.01	0.94–1.08	1.0000
Peritonectomy	**741** (28,208)	2.6%	**118** (12,412)	0.95%	0.36	0.29–0.43	**< 0.0001**
HIPEC	**568** (25,321)	2.2%	**21** (11,204)	0.19%	0.08	0.05–0.13	**< 0.0001**
Colon resection	**1,224** (28,208)	4.3%	**623** (13,617)	4.6%	1.06	0.95–1.67	1.0000
Adrenalectomy	**252** (28,208)	0.9%	**53** (12,409)	0.4%	0.48	0.35–0.64	**< 0.0001**

Adjunctivetherapy	Total gastrectomy and esophageal resection (TE)						
	< 75 y		≥ 75 y				
	n	%	n	%	OR	$CI_{95\%}$	p-value
Pancreatic resection	**147** (2,493)	5.9%	**41** (863)	4.8%	0.79	0.54–1.14	1.0000
Liver resection	**179** (2,493)	8.4%	**77** (919)	7.2%	1.18	0.88–1.57	1.0000
Splenectomy	**317** (2,493)	12.7%	**119** (973)	12.2%	0.96	0.76–1.20	1.0000
Peritonectomy	**75** (2,279)	3.2%	**0** (161)	0.0%	–	–	0.1801
HIPEC	**33** (1,316)	2.5%	**0** (471)	0.0%	–	–	**0.0014**
Colon resection	**114** (2,493)	4.6%	**36** (812)	4.4%	0.97	0.64–1.43	1.0000
Adrenalectomy	**42** (2,149)	2.0%	**3** (592)	0.5%	0.26	0.05–0.80	0.2136

ST, subtotal gastrectomy; T, total gastrectomy; TE, total gastrectomy in combination with esophageal resection; HIPEC, hyperthermic intraperitoneal chemotherapy; <75 y, patients younger than 75 years; ≥75 y, patients at an age of 75 years or more; n, absolute number of patients; the numbers in brackets delineate the overall collective after indexing by the Statistical Office; OR, odds ratio; CI95%, 95% confidence interval; Fisher's exact test with the Bonferroni adjustment of p-values was used for statistical testing. The level of significance was set at 5%.

The bold values denote statistical significance at P <0.05 level.

TABLE 3 Intraoperative and postoperative general and surgical complications in elderly patients undergoing oncological gastric resection in Germany between 2008 and 2018.

A Intraoperative	Subtotal gastrectomy (ST)							Total gastrectomy (T)							Total gastrectomy and esophageal resection (TE)						
	< 75 y		≥ 75 y					< 75 y		≥ 75 y					< 75 y		≥ 75 y				
	n	%	n	%	OR	$CI_{95\%}$	p-value	n	%	n	%	OR	$CI_{95\%}$	p-value	n	%	n	%	OR	$CI_{95\%}$	p-value
Unintended intraoperative damage to vessels or organs	**128** (10,587)	1.2%	**193** (11,207)	1.7%	1.43	1.14–1.81	**0.0173**	**486** (28,208)	1.7%	**298** (13,617)	2.2%	1.28	1.10–1.48	**0.0109**	**50** (2,174)	2.3%	**17** (467)	3.6%	1.60	0.85–2.86	0.9378
Intraoperative bleeding	**474** (10,587)	4.5%	**543** (11,207)	4.8%	1.09	0.96–1.24	1.0000	**1,236** (28,208)	4.4%	**677** (13,617)	5.0%	1.14	1.04–1.26	0.0676	**139** (2,341)	5.9%	**54** (812)	6.7%	1.13	0.80–1.57	1.0000
Interruption of the planned procedure	**30** (5,488)	0.5%	**35** (7,193)	0.49%	0.89	0.53–1.50	1.0000	**87** (28,208)	0.3%	**43** (9,987)	0.4%	1.40	0.95–2.04	0.7965	**0** (924)	0.0%	**0** (450)	0.0%	–	–	–

B Postoperative general	Subtotal gastrectomy (ST)							Total gastrectomy (T)							Total gastrectomy and esophageal resection (TE)						
	<75 y		≥75 y					<75 y		≥75 y					<75 y		≥75 y				
	n	%	n	%	OR	$CI_{95\%}$	p-value	n	%	n	%	OR	$CI_{95\%}$	p-value	n	%	n	%	OR	$CI_{95\%}$	p-value
Apoplexy	**55** (8,656)	0.64%	**122** (11,207)	1.1%	1.72	1.24–2.41	**0.0275**	**106** (28,208)	0.38%	**99** (13,617)	0.73%	1.94	1.46–2.58	0.1081	**10** (1,399)	0.71%	**3** (738)	0.41%	0.57	0.09–2.21	1.0000
Need for resuscitation	**160** (10,587)	1.5%	**293** (11,207)	2.6%	1.75	1.44–2.14	**< 0.0001**	**479** (28,208)	1.7%	**457** (13,617)	3.4%	2.01	1.76–2.29	**< 0.0001**	**69** (2,341)	2.9%	**51** (919)	5.5%	1.93	1.30–2.84	**0.0218**
Myocardial infarction	**206** (10,587)	1.9%	**356** (11,207)	3.2%	1.65	1.39–1.98	**< 0.0001**	**629** (28,208)	2.2%	**535** (13,617)	3.9%	1.79	1.59–2.02	**< 0.0001**	**80** (2,493)	3.2%	**52** (919)	5.7%	1.81	1.23–2.21	0.0642
Cardiac dysrhythmia	**167** (10,587)	1.6%	**435** (11,207)	3.9%	2.52	2.10–3.04	**< 0.0001**	**571** (28,208)	2.0%	**544** (13,617)	4.0%	2.01	1.78–2.27	**< 0.0001**	**91** (2,493)	3.7%	**56** (902)	6.2%	1.75	1.22–2.49	0.0762
Acute myocardial failure	**219** (10,587)	2.1%	**714** (11,207)	6.4%	3.22	2.76–3.77	**< 0.0001**	**488** (28,208)	1.7%	**803** (13,617)	5.9%	3.56	3.17–4.00	**< 0.0001**	**44** (2,279)	1.9%	**66** (866)	7.6%	4.19	2.79–6.34	**< 0.0001**
Pulmonary embolism	**167** (10,587)	1.6%	**195** (11,207)	1.7%	1.10	0.89–1.37	1.0000	**523** (28,208)	1.9%	**261** (13,617)	1.9%	1.03	0.88–1.20	1.0000	**65** (2,070)	3.1%	**22** (733)	3.0%	0.95	0.55–1.58	1.0000
Respiratory failure	**1092** (10,587)	10.3%	**1,595** (11,207)	14.2%	1.44	1.32–1.57	**< 0.0001**	**3,407** (28,208)	12.1%	**2,420** (13,617)	17.8%	1.57	1.48–1.67	**< 0.0001**	**489** (2,493)	19.6%	**249** (973)	25.6%	1.41	1.17–1.68	**0.0054**
Need for tracheostomy	**231** (10,587)	2.2%	**273** (11,207)	2.4%	1.12	0.93–1.34	1.0000	**778** (28,208)	2.8%	**515** (13,617)	3.8%	1.39	1.23–1.55	**< 0.0001**	**128** (2,493)	5.1%	**65** (973)	6.7%	1.32	0.95–1.81	1.0000
Need for prolonged intubation	**29** (7,848)	0.37%	**27** (5,110)	0.53%	1.43	0.81–2.51	1.0000	**101** (25,813)	0.39%	**54** (9,915)	0.54%	1.39	0.98–1.96	1.0000	**17** (1,759)	0.97%	**3** (446)	0.67%	0.69	0.12–2.42	1.0000
Liver dysfunction	**466** (10,587)	4.4%	**548** (11,207)	4.9%	1.11	0.98–1.27	1.0000	**1,428** (28,208)	5.1%	**832** (13,617)	6.1%	1.22	1.11–1.33	**< 0.0001**	**159** (2,493)	6.4%	**53** (764)	6.9%	1.09	0.77–1.52	1.0000

(Continued)

TABLE 3 Continued

B Postoperative general	Subtotal gastrectomy (ST)							Total gastrectomy (T)							Total gastrectomy and esophageal resection (TE)						
	<75 y		≥75 y					<75 y		≥75 y					<75 y		≥75 y				
	n	%	n	%	OR	CI$_{95\%}$	p-value	n	%	n	%	OR	CI$_{95\%}$	p-value	n	%	n	%	OR	CI$_{95\%}$	p-value
Acute renal insufficiency	**530** (10,587)	5.0%	**1,077** (11,207)	9.6%	2.02	1.80–2.25	**< 0.0001**	**1,406** (28,208)	5.0%	**1,422** (13,617)	10.4%	2.22	2.06–2.40	**< 0.0001**	**198** (2,493)	7.9%	**131** (973)	13.5%	1.80	1.41–2.29	**0.0001**
Infection	**1,152** (10,587)	10.9%	**1,826** (11,207)	16.3%	1.59	1.47–1.73	**< 0.0001**	**3124** (28,208)	11.1%	**2,157** (13,617)	15.8%	1.51	1.42–1.60	**< 0.0001**	**301** (2,493)	12.1%	**166** (973)	17.1%	1.50	1.21–1.85	**0.0058**

C gastrectomy (ST)	Total gastrectomy (T)							Total gastrectomy and esophageal resection (TE)													
	<75 y		≥75 y					<75 y		≥75 y					<75 y		≥75 y				
	n	%	n	%	OR	CI$_{95\%}$	p-value	n	%	n	%	OR	CI$_{95\%}$	p-value	n	%	n	%	OR	CI$_{95\%}$	p-value
Need for blood transfusion	**2,918** (8,348)	35.0%	**4,987** (8,951)	55.7%	2.34	2.20–2.49	**< 0.0001**	**8,563** (22,547)	38.0%	**6,323** (11,204)	56.4%	2.12	2.02–2.22	**< 0.0001**	**835** (2,174)	38.4%	**468** (862)	54.3	1.90	1.61–2.24	**< 0.0001**
Bowel obstruction	**184** (10,587)	1.7%	**218** (11,207)	1.9%	1.12	0.91–1.37	1.0000	**354** (28,208)	1.3%	**176** (13,617)	1.3%	1.03	0.85–1.24	1.0000	**20** (1,565)	1.3%	**10** (619)	1.6%	1.27	0.53–2.86	1.0000
Bowel perforation	**47** (9,443)	0.5%	**94** (11,207)	0.84%	1.69	1.17– 2.46	0.0882	**194** (28,208)	0.69%	**153** (13,617)	1.1%	1.64	1.32–2.04	**0.0002**	**11** (1,357)	0.81%	**0** (159)	0.0%	–	–	1.0000
Duodenal leak	**23** (6,660)	0.35%	**24** (6,239)	0.38%	1.11	0.60–2.07	1.0000	**22** (15,675)	0.14%	**25** (7,403)	0.34%	2.41	1.30–4.49	0.0826	**3** (1,312)	0.23%	**3** (914)	0.33%	1.44	0.19–10.7	1.0000
Anastomotic leakage[1]	**281** (5,405)	5.2%	**313** (5,960)	5.3%	1.01	0.85–1.19	1.0000	**1,090** (14,813)	7.4%	**756** (7,691)	9.8%	1.37	1.24–1.51	**< 0.0001**	**182** (1,741)	10.4%	**85** (704)	12.1%	1.18	0.88–1.56	1.0000
Pancreatic fistula	**563** (10,587)	5.3%	**559** (11,207)	5.0%	0.93	0.82–1.06	1.0000	**1,796** (28,208)	6.4%	**818** (13,617)	6.0%	0.94	0.86–1.02	1.0000	**193** (2,493)	7.7%	**64** (919)	7.0%	0.89	0.65–1.20	1.0000
Pancreatitis	**45** (8,679)	0.52%	**32** (8,279)	0.39%	0.74	0.45–1.20	1.0000	**115** (28,208)	0.41%	**66** (13,617)	0.48%	1.19	0.86–1.63	1.0000	**7** (1,392)	0.5%	**0** (667)	0.0%	–	–	1.0000
Need for abdominal drainage	**397** (10,587)	3.7%	**433** (11,207)	3.9%	1.03	0.89–1.19	1.0000	**1,144** (28,208)	4.0%	**619** (13,617)	4.5%	1.12	1.01–1.25	0.6243	**129** (2,493)	5.2%	**49** (737)	6.6%	1.31	0.90–1.85	1.0000
Impaired gastric emptying	**3** (3,876)	0.08%	**16** (6,144)	0.26%	3.37	0.96–18.07	1.0000	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other complications	**1,904** (10,587)	18.0%	**2183** (11,207)	19.5%	1.10	1.02–1.18	0.1473	**5,461** (28,208)	19.4%	**2,969** (13,617)	21.8%	1.16	1.10–1.22	**< 0.0001**	**576** (2,493)	23.1%	**233** (973)	23.9%	1.05	0.88–1.25	1.0000

ST, subtotal gastrectomy; T, total gastrectomy; TE, total gastrectomy in combination with esophageal resection; <75 y, patients younger than 75 years; ≥75 y, patients at an age of 75 years or more; n, absolute number of patients; the numbers in brackets delineate the overall collective after indexing by the Statistical Office; OR, odds ratio; CI$_{95\%}$, 95% confidence interval; [1]The ICD-10-GM code for anastomotic leakage was just introduced in 2013; Fisher's exact test with the Bonferroni adjustment of p-values was used for statistical testing. The level of significance was set at 5%.
The bold values denote statistical significance at P < 0.05 level.

10.3389/fonc.2022.1032443

TABLE 4 In-hospital mortality following oncological gastric surgery in elderly patients in Germany between 2008 and 2018.

	< 75 y			≥ 75 y					
	n	In-hospital death	Mortality	n	In-hospital death	Mortality	OR	$CI_{95\%}$	p-value
ST	10,587	462	4.36%	11,207	1,233	11.0%	2.71	2.42–3.03	<0.0001
T	28,208	1,193	4.23%	13,617	1,618	11.9%	3.05	2.82–3.30	<0.0001
TE	2,493	146	5.86%	916	127	13.9%	2.59	1.99–3.35	<0.0001

ST, subtotal gastrectomy; T, total gastrectomy; TE, total gastrectomy in combination with esophageal resection; <75 y, patients younger than 75 years; ≥75 y, patients at an age of 75 years or more; n, absolute number of patients; OR, odds ratio; $CI_{95\%}$: 95% confidence interval, Fisher's exact test with the Bonferroni adjustment of p-values was used for statistical testing. The level of significance was set at 5%.

Discussion

The present study assessed differences in outcome after major oncologic gastric surgery among patients aged 75 years and older in Germany between 2008 and 2018 based on the G-DRG database of the German Federal Statistical Office (DESTATIS). Significant differences were found in particular with respect to postoperative morbidity and mortality.

Comorbidity was measured using the Charlson comorbidity index. The elderly collective scored significantly higher compared to younger patients stratified by each kind of gastric resection and each single year under study. Obviously, the difference is biased by the fact that the age of a particular patient is part of the calculation formula for the Charlson comorbidity index itself. An age between 80 and 89 years adds 4 points to the score, and an age of more than 90 years contributes to even 5 points, respectively. Nevertheless, the mean score suggests a 10-year mortality of 47% in the L75 group and 79% in the G75 collective solely based on comorbidity profile without considering the surgeries performed, indicating a certain vulnerability among the elderly group (12). For this reason, especially if life expectancy is reached, preoperative comorbidities and clinical circumstances must thoroughly be taken into account when planning major gastric resection for cancer in elderly patients.

The pattern of reconstruction techniques was rather similar in both groups. Merely after ST, there were more BII-like reconstructions performed in the elderly, and, after T, a slightly increased rate of reconstruction techniques 'other than BII and RY' was seen in this group. All in all, the age does not influence the choice of reconstruction technique fundamentally. Unfortunately, the current version of the OPS does not reflect the whole range of possible reconstruction techniques in detail. As case numbers in western Europe are not comparable to that in Asia, the implementation of new reconstruction approaches and their representation in the relevant coding systems are still hampered (13).

Regarding LAD, straight D2 and D3 LAD seems to be applied less frequently to elderly patients. Instead, other strategies like partial D2 or D3 LAD are more common in this group (see the supplement for the exact code definition used for the query). The fact that LAD is performed to an altered extent in elderly gastric cancer patients is already known and has been shown to be appropriate in Asian populations (14). The influence on the clinical outcome of adapted LAD in elderly patients in a western collective cannot fully be uncovered by the presented study. However, recent research suggests that standard D2 gastrectomy can safely be applied even to elderly patients (15, 16). Further research and clear recommendations are urgently needed on this field, as the presented data suggest, that D2 LAD seems to be applied hesitantly to patients older than 75 years, which may influence the oncologic outcome. Nonetheless, D2 dissection rates were surprisingly low although D2 LAD was adopted as a standard surgical procedure in the local guidelines. It may be speculated that D2 is either not performed according to the guideline recommendations or that the coding was not done appropriately. The influence of modified LAD on postoperative outcomes, therefore, cannot be finally evaluated in the setting of this analysis.

Another indicator of an adapted approach in elderly patients is the lower rate of additive organ resections such as pancreatic resection and peritonectomy. In addition, HIPEC is applied less frequently to the G75 collective. A less aggressive approach in gastric surgery for the elderly has been observed previously, as a reduction in the dimension of treatment may significantly improve the complication profile and should be considered in these patients (17). The data indicate an already-present clear consideration about the kind and extent of adjunctive surgery in daily clinical practice. Thus, pancreatic resection in the case of ST and T and adrenalectomy alongside T represent the only significantly altered organ resection approaches applied to elderly patients. The rates of colon and liver resection as well as splenectomy are not significantly divergent compared to younger patients.

Aside from a slightly increased rate of unintended damaging of blood vessels and organs, there appears to exist no significant influence of advanced age on the immediate intraoperative course. Bleeding during surgery and the interruption of the planned procedure are not impacted. Of course, a possibly explorative intent of a surgery cannot be deduced ultimately from the presented data. Even the postoperative surgical course seems only to be influenced by three particular aspects, namely, the necessity of blood transfusions, a higher rate of bowel perforation, and anastomotic leakage after total gastrectomy, aside from an increase in 'other complications' (see the supplement for code definition). However, we cannot derive the actual reason for a higher rate of transfusions from the data. As intraoperative bleeding seems not to be responsible, there may be other aspects like a decreased ability for compensation in the presence of low hemoglobin values among the elderly group. As already mentioned above in terms of comorbidity, a preoperative assessment of anemia and age-appropriate management could improve the outcome and avoid the extensive use of blood transfusions (18). Regarding the increased incidence of anastomotic leakage after total gastrectomy in the elderly, nutritional aspects and comorbidity may be important factors and further research is required to overcome this life-threatening adverse event (19).

Non-surgical complications like respiratory, renal or myocardial failure, and the need for cardio pulmonary resuscitation (CPR) in case of cardiac arrest are significantly increased in the elderly. Moreover, the distinct susceptibility to postoperative infections must be taken into account. However, there are preoperative screening tools available or currently under development addressing this problem; there is an urgent need for further improvement (20–23). In this sense, even an appropriate assessment of the mentioned postoperative complications and adverse events with clear recommendations would be helpful to minimize morbidity.

Regarding postoperative mortality, there was a more-than-doubled probability of in-hospital death in the elderly collective. The rates of 11%–13%, depending on the extent of resection, highlight once again the vulnerability of that group compared to younger patients and raise the question of whether less invasive surgery might be of advantage in the selected subgroups of this collective. However, a meta-analysis by Kong et al. did not show a difference regarding morbidity and mortality between T and ST without regard on age; the extent of resection seems to be relevant in elderly patients (24).

There exist several limitations in the presented study regarding data quality and the informative value. The necessity to avoid small group sizes in the query strategy for the G-DRG database to minimize the probability of indexing by the Statistical Office for secrecy reasons delimits the grade of detail, like the particular strategy of LAD in each subgroup. Furthermore, only morbidity and procedures operationalized within the ICD-10 and OPS are evaluable. For example, there exists no information about the histological subtype of a tumor if not explicitly defined in the particular code. Our intent to use the international consensus list of complications after gastrectomy could not be realized ultimately as the pieces of information cannot be derived from the DESTATIS database (10). Finally, the quality of data depends highly on the sincerity of the encoding personnel in the hospitals, and economical interests may bias the data to a certain degree. Aside from this, it may not be deducted from the data presented if patients died from aggressive or progressing tumor burden or the complication itself. This fact further limits the generalizability of the data presented.

All in all, the impact of age on the perioperative outcome of patients undergoing gastrectomy is still controversial and cannot be fully uncovered by the present data. Varying endpoints and cutoffs in recent studies further complicate a comprehensive overview of the underlying issues. For instance, a cutoff age of 45 years with the definition that patients older than 45 years are 'elderly' in an exemplary study by Cheng et al. in 2021 suggests that there exists no difference between young and older patients during and after gastrectomy regarding several complications contrarily to our results (25). On the other hand, there exist several publications that confirm our impression of a significant impact of age on the postoperative outcome after gastrectomy (8, 26). Many articles about elderly patients already indicate a general consideration of geriatric aspects in major gastric surgery as this group is obviously more susceptible to numerous complications. Nevertheless, further systematic investigation is mandatory as there do not exist valid and comprehensive recommendations regarding a reasonable balance between surgical extent and the oncological outcome in the western collectives of elderly patients with gastric cancer yet.

Conclusion

The presented results demonstrate that the immediate outcome of major oncological gastric surgery depends highly on age aspects. Elderly patients have a tremendously increased likelihood of in-hospital morbidity and mortality, a fact that must be considered thoroughly when planning gastric resection. Nonetheless, the present data allow a real-life evaluation of all surgical gastric cancer cases in Germany and should be respected when counseling patients to decide for further therapeutic steps. Further research and new approaches to individualized geriatric surgery for gastrectomy are urgently needed in that sense.

Data availability statement

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

Author contributions

MB: Programming of the query to the Federal Statistical Office of Germany, data evaluation, statistical analysis, literature review, manuscript writing M-CW: data evaluation, statistical analysis, literature review, manuscript writing P-AN: data evaluation, statistical analysis, literature review, manuscript writing HF: data evaluation, statistical analysis, literature review, manuscript writing DR: data evaluation, statistical analysis, literature review, manuscript writing. All authors contributed to the article and approved the submitted version.

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.2022.1032443/full#supplementary-material

References

1. Neumann PA, Berlet MW, Friess H. Surgical oncology in the age of multimodality therapy for cancer of the upper and lower gastrointestinal tract. *Expert Rev Anticancer Ther* (2021) 21(5):511–22. doi: 10.1080/14737140.2021.1868991

2. Tan KK, Quek TJ, Wong N, Li KK, Lim KH. Early outcome following emergency gastrectomy. *Ann Acad Medicine-Singapore* (2012) 41(10):451. doi: 10.47102/annals-acadmedsg.V41N10p451

3. Seo SH, Hur H, An CW, Yi X, Kim JY, Han SU, et al. Operative risk factors in gastric cancer surgery for elderly patients. *J gastric cancer* (2011) 11(2):116–21. doi: 10.5230/jgc.2011.11.2.116

4. Katai H, Sasako M, Sano T, Maruyama K. The outcome of surgical treatment for gastric carcinoma in the elderly. *Japanese J Clin Oncol* (1998) 28(2):112–5. doi: 10.1093/jjco/28.2.112

5. Shimada S, Sawada N, Oae S, Seki J, Takano Y, Ishiyama Y, et al. Safety and curability of laparoscopic gastrectomy in elderly patients with gastric cancer. *Surg Endosc* (2018) 32(10):4277–83. doi: 10.1007/s00464-018-6177-1

6. Wang J-f, Zhang S-z, Zhang N-y, Wu Z-y, Feng J-y, Ying L-p, et al. Laparoscopic gastrectomy versus open gastrectomy for elderly patients with gastric cancer: a systematic review and meta-analysis. *World J Surg Oncol* (2016) 14(1):1–10. doi: 10.1186/s12957-016-0859-8

7. Garbarino GM, Costa G, Frezza B, Biancafarina A, Balducci G, Mercantini P, et al. Robotic versus open oncological gastric surgery in the elderly: a propensity score-matched analysis. *J Robotic Surg* (2021) 15(5):741–9. doi: 10.1007/s11701-020-01168-2

8. Hayashi T, Yoshikawa T, Aoyama T, Ogata T, Cho H, Tsuburaya A. Severity of complications after gastrectomy in elderly patients with gastric cancer. *World J Surg* (2012) 36(9):2139–45. doi: 10.1007/s00268-012-1653-6

9. RDC of the Federal Statistical Officeand Statistical Offices of the Länder, Diagnosis-Related Group Statistics (DRG Statistics), 2008-2018, own calculations, doi: 10.21242/23141.2018.00.00.1.1.0

10. Baiocchi GL, Giacopuzzi S, Marrelli D, Reim D, Piessen G, Matos da Costa P, et al. International consensus on a complications list after gastrectomy for cancer. *Gastric Cancer* (2019) 22(1):172–89. doi: 10.1007/s10120-018-0839-5

11. R Core Team. *R: A language and environment for statistical computing [Internet]*. Vienna Austria: R Foundation for Statistical Computing (2020). Available at: https://www.R-project.org/.

12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* (1987) 40(5):373–83. doi: 10.1016/0021-9681(87)90171-8

13. Weber MC, Berlet M, Novotny A, Friess H, Reim D. [Reconstruction following gastrectomy]. *Chirurg.* (2021) 92(6):506–14. doi: 10.1007/s00104-020-01350-0

14. Endo S, Fujiwara Y, Higashida M, Kubota H, Matsumoto H, Tanaka H, et al. Is D2 lymphadenectomy necessary in elderly gastric cancer patients? a retrospective study. *Int Surg* (2022). doi: 10.9738/INTSURG-D-22-00001.1

15. Jeong O, Park YK, Ryu SY, Kim YJ. Effect of age on surgical outcomes of extended gastrectomy with D2 lymph node dissection in gastric carcinoma: Prospective cohort study. *Ann Surg Oncol* (2010) 17(6):1589–96. doi: 10.1245/s10434-010-0916-4

16. Back J, Sallinen V, Kokkola A, Puolakkainen P. Surgical and oncological outcomes of D1 versus D2 gastrectomy among elderly patients treated for gastric cancer. *Scand J Surg* (2022) 111(2):14574969221096192. doi: 10.1177/14574969221096193

17. Chen ZX, Li J, Liu WB, Zhang SR, Sun H. Elemene-containing hyperthermic intraperitoneal chemotherapy combined with chemotherapy for elderly patients with peritoneal metastatic advanced gastric cancer. *World J Clin Cases* (2022) 10 (5):1498–507. doi: 10.12998/wjcc.v10.i5.1498

18. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol* (2014) 89(1):88–96. doi: 10.1002/ajh.23598

19. Makuuchi R, Irino T, Tanizawa Y, Bando E, Kawamura T, Terashima M. Esophagojejunal anastomotic leakage following gastrectomy for gastric cancer. *Surg Today* (2019) 49(3):187–96. doi: 10.1007/s00595-018-1726-8

20. Hamakawa T, Kurokawa Y, Mikami J, Miyazaki Y, Takahashi T, Yamasaki M, et al. Risk factors for postoperative complications after gastrectomy in gastric cancer patients with comorbidities. *Surg Today* (2016) 46(2):224–8. doi: 10.1007/s00595-015-1175-6

21. Aceto P, Antonelli Incalzi R, Bettelli G, Carron M, Chiumiento F, Corcione A, et al. Perioperative management of elderly patients (PriME): recommendations from an Italian intersociety consensus. *Aging Clin Exp Res* (2020) 32(9):1647–73. doi: 10.1007/s40520-020-01624-x

22. Hirahara N, Tajima Y, Fujii Y, Kaji S, Kawabata Y, Hyakudomi R, et al. Prediction of postoperative complications and survival after laparoscopic gastrectomy using preoperative geriatric nutritional risk index in elderly gastric cancer patients. *Surg Endosc* (2021) 35(3):1202–9. doi: 10.1007/s00464-020-07487-7

23. Endo S, Yamatsuji T, Fujiwara Y, Higashida M, Kubota H, Matsumoto H, et al. Prognostic factors for elderly gastric cancer patients who underwent gastrectomy. *World J Surg Onc* (2022) 20(1):10. doi: 10.1186/s12957-021-02475-0

24. Kong L, Yang N, Shi L, Zhao G, Wang M, Zhang Y. Total versus subtotal gastrectomy for distal gastric cancer: meta-analysis of randomized clinical trials. *Onco Targets Ther* (2016) 9:6795–800. doi: 10.2147/OTT.S110828

25. Cheng YX, Tao W, Liu XY, Yuan C, Zhang B, Zhang W, et al. The outcome of young vs. old gastric cancer patients following gastrectomy: a propensity score matching analysis. *BMC Surg* (2021) 21(1):399. doi: 10.1186/s12893-021-01401-1

26. Hager ES, Abdollahi H, Crawford AG, Moudgill N, Rosato EL, Chojnacki KA, et al. Is gastrectomy safe in the elderly? a single institution review. *Am Surgeon* (2011) 77(4):488–92. doi: 10.1177/000313481107700429

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 17 January 2023
DOI 10.3389/fonc.2023.970187

Protein-energy malnutrition and worse outcomes after major cancer surgery: A nationwide analysis

Jiewen Jin[1†], Xianying Zhu[2†], Zhantao Deng[3†], Pengyuan Zhang[1], Ying Xiao[2], Hedong Han[4], Yanbing Li[1*] and Hai Li[1*]

[1]Department of Endocrinology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China, [2]Department of Intensive Care Unit, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China, [3]Department of Orthopedics, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China, [4]Department of Respiratory and Critical Care Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China

Check for updates

OPEN ACCESS

EDITED BY
Lucia Moletta,
University of Padua, Italy

REVIEWED BY
Lidia Santarpia,
University of Naples Federico II, Italy
Antonio Simone Laganà,
University of Palermo, Italy

*CORRESPONDENCE
Hai Li
lihai8@mail.sysu.edu.cn
Yanbing Li
liyb@mail.sysu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 15 June 2022
ACCEPTED 03 January 2023
PUBLISHED 17 January 2023

CITATION
Jin J, Zhu X, Deng Z, Zhang P, Xiao Y, Han H, Li Y and Li H (2023) Protein-energy malnutrition and worse outcomes after major cancer surgery: A nationwide analysis.
Front. Oncol. 13:970187.
doi: 10.3389/fonc.2023.970187

Background: Protein-energy malnutrition (PEM) has been recognized as a poor prognostic factor in many clinical issues. However, nationwide population studies concerning the impact of PEM on outcomes after major cancer surgery (MCS) are lacking. We aimed to evaluate the postoperative outcomes associated with PEM following MCS.

Methods: By using the Nationwide Inpatient Sample database, data of patients undergoing MCS including colectomy, cystectomy, esophagectomy, gastrectomy, hysterectomy, lung resection, pancreatectomy, or prostatectomy were analyzed retrospectively from 2009 to 2015, resulting in a weighted estimate of 1,335,681 patients. The prevalence trend of PEM, as well as mortality and major complications after MCS were calculated. Multivariable regression analysis was applied to estimate the impact of PEM on postoperative outcomes after MCS.

Results: PEM showed an estimated annual percentage increase of 7.17% (95% confidence interval (CI): 4-10.44%) from 2009 to 2015, which contrasts with a 4.52% (95% CI: -6.58–2.41%) and 1.21% (95% CI: -1.85–0.56%) annual decrease in mortality and major complications in patients with PEM after MCS. PEM was associated with increased risk of mortality (odds ratio (OR)=2.26; 95% CI: 2.08-2.44; $P < 0.0001$), major complications (OR=2.46; 95% CI: 2.36-2.56; $P < 0.0001$), higher total cost ($35814 [$22292, $59579] vs. $16825 [$11393, $24164], $P < 0.0001$), and longer length of stay (14 [9-21] days vs. 4 [2-7] days, $P < 0.0001$), especially in patients underwent prostatectomy, hysterectomy and lung resection.

Conclusions: PEM was associated with increased worse outcomes after major cancer surgery. Early identification and timely medical treatment of PEM for patients with cancer are crucial for improving postoperative outcomes.

KEYWORDS

protein-energy malnutrition (PEM), major cancer surgery, mortality, postoperative complications, nationwide analysis

1 Introduction

Protein-energy malnutrition (PEM), caused by depleted energy and nutrient stores, often leads to alterations in body weight and composition and compromised functioning (1). PEM has been recognized as a poor prognostic factor in many clinical issues, such as acute myocardial infarction, sepsis, and heart failure (1–3). Consequently, the importance of identification and management of PEM has been highlighted in recent years.

Cancer is a major public health problem worldwide and has been the second leading cause of death in the United States (4). In China, cancer death accounted for 24% of all-cause of death during 2014 to 2018 and is the leading cause of death in the population less than 65 years old (5). Metabolic diseases, such as obesity and diabetes, are vital risk factors for cancers, which may resulted from energy imbalance and inflammation (6, 7). Patients with cancer are at a particularly high risk of malnutrition. The etiology is complicated, including impaired food intake due to host and therapeutic factors, increased energy and protein demands, and metabolic abnormalities (8). Although there is a relatively high prevalence of malnutrition ranging from 20% to more than 70% in patients with cancer, only 30-60% of those at risk of malnutrition received nutritional support (8).

Surgery, one of the major cancer treatments, can negatively regulate nutrition status due to the catabolic impact of the surgery itself, inflammation induction, and enhanced metabolic stress response (9). Malnutrition is associated with negative clinical outcomes following certain cancer surgeries such as esophagectomy, gastrectomy, colectomy, hepatectomy, pancreatectomy, lung resection, cystectomy, and hysterectomy (10–16). However, nationwide population studies on the impact of PEM on outcomes after major cancer surgery (MCS) are lacking.

Therefore, we used National Inpatient Sample (NIS) database to explore: 1) prevalence and temporal trends of PEM who underwent MCS; 2) the impact of PEM on mortality, major complications, total cost, and length of stay (LOS) after MCS; 3) the influence of surgical type on the perioperative outcomes of PEM patients.

2 Methods

2.1 Data source and study population

It is a retrospective cohort study investigating the influence of PEM on perioperative outcomes in patients undergoing MCS. Patients aged 18-90 years old who were admitted between January 1st, 2009 to December 31st, 2015 and primarily for MCS were included from NIS database. The NIS database is the largest all-payer administrative database that includes a 20% stratified sample of United States inpatient hospitalizations from nonfederal community hospitals (17). The NIS database provides information including patient features, primary diagnosis, up to 29 secondary diagnoses, up to 15 inpatient procedures, hospitalization costs, and LOS (1). We selected a total of eight major surgical oncological procedures (colectomy, cystectomy, esophagectomy, gastrectomy, hysterectomy, lung resection, pancreatectomy, and prostatectomy) as MCS and evaluated their perioperative outcomes. Relying on specific International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes, each surgical procedure was assessed independently, and analyses were restricted to cancer diagnoses only (Supplementary Table 1) (18).

2.2 Ethical approval

The data collected in the present study is from an open access database, where the ethics approval and consent to participated had been made when the database setup. Hence, it is not applicable in the present study.

2.3 Outcomes

The primary outcome was perioperative outcomes, which included mortality, major complications, total costs, and LOS. Mortality, total costs, and LOS were directly extracted from NIS database. Major complications were identified through ICD-9-CM diagnosis codes, defined as pneumonia, pulmonary embolism, renal failure, acute ischemic stroke, acute myocardial infarction, cardiac arrest, adult respiratory distress syndrome, sepsis, and septic shock (Supplementary Table 2).

2.4 Predictor

PEM (primary predictor) was identified with ICD-9-CM diagnosis codes (260, 261, 262, 263, 2698, 7994, 7833, 7837, 78321, 78322), which included kwashiorkor, marasmus, cachexia, other severe protein-calorie malnutrition (severe and unspecified), adult failure to thrive, loss of weight, and underweight. These set of diagnosis codes is recommended by the Academy of Nutrition and Dietetics, and the American Society for Parenteral and Enteral Nutrition and have been used by many studies (1–3, 19).

2.5 Patient and hospital characteristics

For all patients, the following independent variables were potential confounders and were available for analyses: patient age at hospitalization, sex, elective status, race (white, black, Hispanic, other (Asian, Pacific Islander, or Native American), or unknown), insurance status, income quartile, hospital type, hospital region, hospital bed size, baseline comorbidities, and type of cancer surgery. All the potential confounders were identified either as already present in NIS database or clinical classification software codes to abstract them from the diagnosis variables (2).

Patient age was regarded as a continuous variable. Insurance categories included Medicare, Medicaid, private insurance, and other insurance types (self-pay). Income was stratified into four quartiles based on the average annual household income of the zip code of residence (0-25th, 26-50th, 51-75th, and 76-100th quartiles). The hospital type was categorized by the hospital's teaching status (rural, urban non-teaching, and teaching). The Hospital region included the Northeast, Midwest, South, and West regions.

Hospitals bed size was stratified as small, medium and large hospital size (20). Baseline comorbidities were quantified using an Elixhauser comorbidity index (ECI) (21). Elixhauser comorbid conditions included: alcohol abuse, acquired immune deficiency syndrome, deficiency anemias, rheumatoid arthritis/collagen vascular diseases, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes without complications, diabetes with chronic complications, drug abuse, hypertension (uncomplicated and complicated), hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, obesity, other neurological disorders, paralysis, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, peptic ulcer disease excluding bleeding, valvular disease, and weight loss (Supplementary Table 3).

2.6 Statistical analysis

All analyses were performed on the provided NIS population (268,595 individuals), and P-values were calculated for the weighted population (1,335,681 individuals). Descriptive statistics were generated on frequencies and proportions of categorical variables (gender, type of admission, race, insurance status, median zip code household income, hospital teaching status, hospital region, hospital bed size, ECI, and type of cancer surgery) and stratified according to PEM occurrence. Means were reported for continuously coded variables (age). Chi-square tests were applied to compare the statistical significance of differences within categorical variables. Temporal trends in rates were analyzed by the estimated annual percent change (EAPC) using linear regression analyses. To further investigate the relationship between PEM and outcomes after MCS, we used multivariable logistic regression models adjusted for age, sex, race, type of insurance, elective status, income quartile, hospital type, hospital region, hospital bed size, ECI, and surgical type. Subgroup analyses stratified by surgical type were applied. Sensitivity analyses were performed to test the robustness of our findings. We reassessed the relationship between PEM and clinical outcomes in patients undergoing MCS based on a double robust inverse probability of treatment weighting method (22). The probability of treatment or propensity score was calculated using multivariable logistic regression models adjusted for the aforementioned variables. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as a P-value < 0.05 on two-tailed testing.

3 Results

3.1 Baseline descriptive statistics

A total of 268,595 (weighted 1,335,681) patients who underwent MCS were selected from 2009 to 2015 of NIS database. Among them, 7.1% of patients had PEM. Patient with PEM were older, more likely to be female, higher percentage of black subjects, more likely to have Medicare as their primary health insurance and a lower income (Table 1). It was not surprising that patients with PEM had a higher comorbidity burden with a greater proportion of patients with ECI ≥ 3 (77.39% vs. 28.78%, P < 0.0001) (Table 1). As shown in Supplementary Table 3, almost all of the Elixhauser comorbid conditions were statistically significant between patients who underwent MCS with and without PEM (P < 0.05 for all).

Concerning the type and admission of surgery, patients with PEM had lower proportion of elective admission (53.38% vs. 85.61%, P < 0.0001) with highest proportion of colectomy (51.44%), followed by pancreatectomy (13.47%), lung resection (12.02%), gastrectomy (9.39%), cystectomy (6.17%), esophagectomy (3.87%), hysterectomy (2.66%) and prostatectomy (0.98%) (Table 1). Patients who underwent operations for gastrointestinal (GI) cancers had the highest prevalence of PEM. Esophageal cancer ranked first (24.6502%), gastric cancer ranked second (22.029%), followed by pancreatic cancer (19.7319%), and colon cancer (15.1097%). Patients treated surgically for lung cancer (4.9766%) and bladder cancer (9.6109%) had moderate rates of PEM. Patients who underwent operations for uterine cancer (1.5188%) and prostate cancer (0.2171%) had the lowest rates of PEM (Figure 1).

3.2 Temporal trends of PEM, mortality and major complications

Over the entire study period, temporal trend analyses showed that the EAPC of PEM was +7.17% (95% confidence interval [CI]: 4-10.44; P = 0.0019) (Figure 2). During the same period, the EAPC of mortality in patients with PEM was -4.52% (95% CI: -6.58–2.41, P < 0.01) while the EAPC of mortality in patients without PEM was -4.21% (95% CI: -6.68–1.68, P < 0.01) (Figure 3). Meanwhile, the EAPC of major complications in patients with PEM was -1.21% (95% CI: -1.85–0.56, P = 0.0048), and the EAPC of major complications in patients without PEM showed no significant change (EAPC = 1.45, 95% CI: -0.43-3.36, P = 0.1046) (Figure 4).

3.3 Perioperative outcomes after MCS in patient with PEM

Patients with PEM had poorer perioperative outcomes after MCS. The mortality rate was 7.77% in patients with PEM, which was 2.26-fold higher than those without PEM (1.19%) (odds ratio [OR]= 2.26, 95% CI: 2.08-2.44, P<0.0001) (Table 2). Moreover, PEM was associated with higher total cost ($35814 vs. $16825, P < 0.0001) and longer LOS (14 days vs. 4 days, P < 0.0001) (Table 2).

Considering major complications, PEM group showed a 2.46-fold increase of risk when compared with non-PEM group (OR=2.46, 95% CI: 2.36-2.56, P < 0.0001) (Table 2). More specifically, renal failure (22.91%), pneumonia (21.64%), adult respiratory distress syndrome (14.23%), and septic shock (10.43%) were most common in the PEM group. When compared with non-PEM group, patients with PEM had higher risk of septic shock (OR=3.55, 95%CI: 3.28-3.86) and sepsis (OR=3.08, 95%CI: 2.82-3.36), followed by pneumonia (OR=2.52, 95% CI: 2.40-2.65), adult respiratory distress syndrome (OR= 2.51, 95%CI: 2.36-2.68), renal failure (OR=1.98, 95%CI: 1.89-2.07), acute ischemic stroke (OR=1.98, 95%CI: 1.68-2.33), cardiac arrest (OR=1.88, 95%CI: 1.61-2.20), pulmonary embolism (OR=1.62, 95%CI: 1.44-1.82) and acute myocardial infarction (OR=1.44, 95%CI: 1.28-1.62). Moreover,

10.3389/fonc.2023.970187

TABLE 1 Baseline characteristics in patients undergoing major cancer surgery with and without PEM.

Variables	With PEM (N=19201, %)	Without PEM (N=249394, %)	P-value
Mean age (SE)	69.67(0.12)	64.92(0.06)	<0.0001
Female	8831(45.99)	94160(37.76)	<0.0001
Elective admission	10250(53.38)	213499(85.61)	<0.0001
Race			<0.0001
White	13051(67.97)	173797(69.69)	
Black	2251(11.72)	24716(9.91)	
Hispanic	1109(5.78)	14459(5.80)	
Other	1061(5.53)	13353(5.35)	
Unknown	1729(9.00)	23069(9.25)	
Type of insurance			<0.0001
Medicare	12542(65.32)	120503(48.32)	
Medicaid	1412(7.35)	12054(4.83)	
Private	4239(22.08)	105314(42.23)	
Others	1008(5.25)	11523(4.62)	
Income quartile			<0.0001
0-25th	5551(28.91)	56643(22.71)	
26-50th	5031(26.20)	61041(24.48)	
51-75th	4556(23.73)	62358(25.00)	
76-100th	4063(21.16)	69352(27.81)	
Hospital type			<0.0001
Rural	1507(7.85)	15244(6.11)	
Urban non-teaching	5711(29.74)	66993(26.86)	
Urban teaching	11983(62.41)	167157(67.03)	
Hospital region			0.0002
Northeast	3229(16.82)	51167(20.52)	
Midwest	5088(26.50)	60821(24.39)	
South	7238(37.70)	89298(35.81)	
West	3646(18.99)	48108(19.29)	
Hospital bed size			0.0247
Small	2040(10.62)	29171(11.70)	
Medium	4525(23.57)	54208(21.74)	
Large	12636(65.81)	166015(66.57)	
ECI			<0.0001
0	41(0.21)	52898(21.21)	
1	1259(6.56)	69003(27.67)	
2	3042(15.84)	55719(22.34)	
≥3	14859(77.39)	71774(28.78)	
Cancer surgical type			<0.0001
Colectomy	9877(51.44)	55450(22.23)	

(Continued)

TABLE 1 Continued

Variables	With PEM (N=19201, %)	Without PEM (N=249394, %)	P-value
Cystectomy	1185(6.17)	11112(4.46)	
Esophagectomy	743(3.87)	2272(0.91)	
Gastrectomy	1803(9.39)	6367(2.55)	
Lung resection	2308(12.02)	43950(17.62)	
Hysterectomy	511(2.66)	33048(13.25)	
Pancreatectomy	2586(13.47)	10513(4.22)	
Prostatectomy	188(0.98)	86682(34.76)	

SE, standard error; ECI, Elixhauser comorbidity index; PEM, protein-energy malnutrition.

patients with PEM showed a 2.62-fold increase in the need for mechanical ventilation after MCS compared with patients without PEM (OR=2.62, 95%CI: 2.47-2.77, P < 0.0001) (Table 2).

3.4 The influence of surgical type on perioperative outcomes

In order to investigate the influence of surgical type on the perioperative outcomes of PEM patients, subgroup analysis was conducted. The rate of mortality varied among surgical types (Supplementary Table 4). PEM patients underwent lung resection (10.27%) and colectomy (8.35%) had the highest mortality rate while those underwent prostatectomy had the lowest mortality (1.6%).

The risk of mortality and major complications also varied among surgical types. Patients with PEM underwent prostatectomy had the highest risk of mortality (OR=13.59, 95%CI: 3.26-56.65), and major complications (OR=7.34, 95%CI: 5.18-10.38), followed by patients underwent hysterectomy (mortality: OR=9.81; major complications, OR=5.38) and lung resection (mortality: OR=4.64; major complications, OR=3.49), which were all non-GI operations (Table 3). On the other hand, gastrointestinal operations, such as colectomy, esophagectomy, gastrectomy, pancreatectomy and cystectomy, had relatively lower risk (1-2 folds) of perioperative mortality in patients with PEM (Table 3).

3.5 Sensitivity analysis

In order to eliminate the influence of residual confounders on the robustness of the results, a sensitivity analysis was conducted. All the results, including mortality, major complications, total costs, and LOS remained statistically significant after the double robust inverse probability of treatment weighting method (Supplementary Table 5).

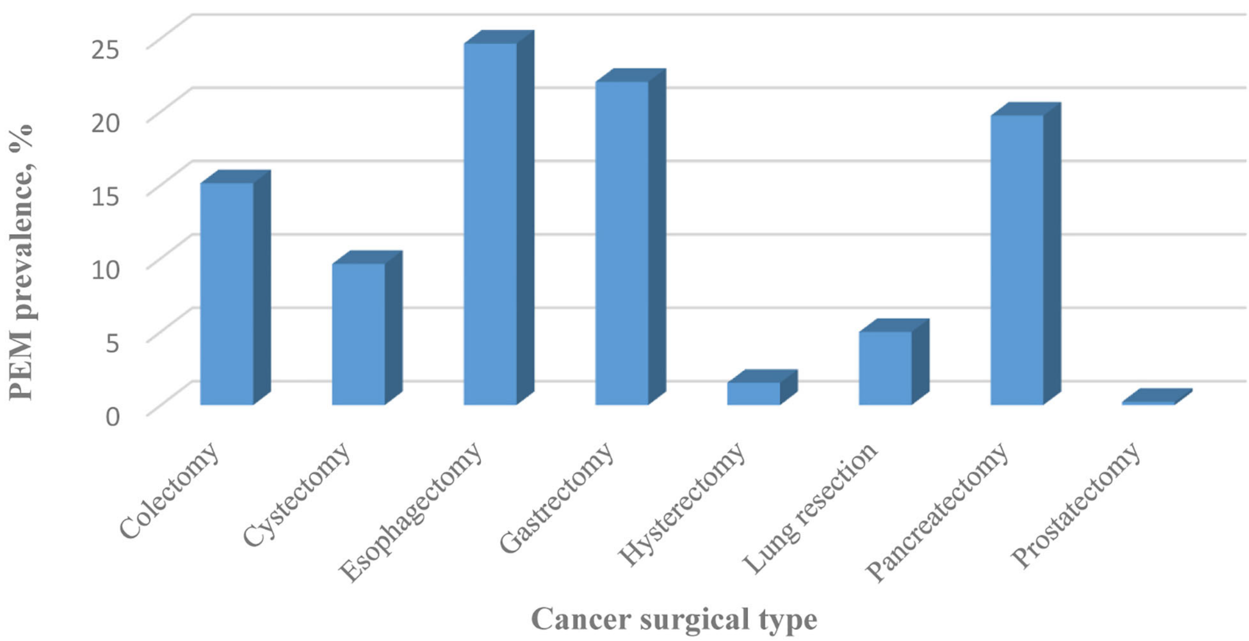


FIGURE 1
Prevalence of PEM classified by cancer surgery type between 2009 and 2015 in the United States.

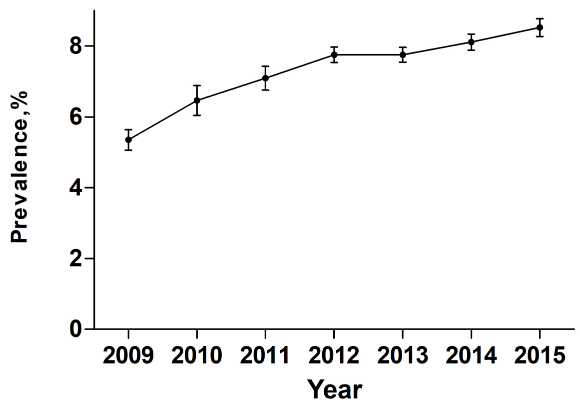


FIGURE 2
Prevalence of PEM in patients undergoing major cancer surgery patients between 2009 and 2015 in the United States.

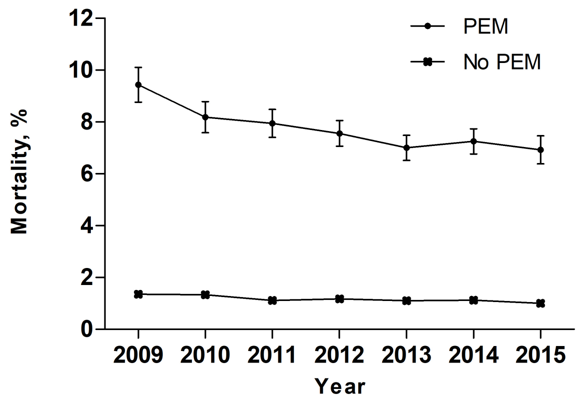


FIGURE 3
Mortality in patients with and without PEM between 2009 and 2015 in the United States.

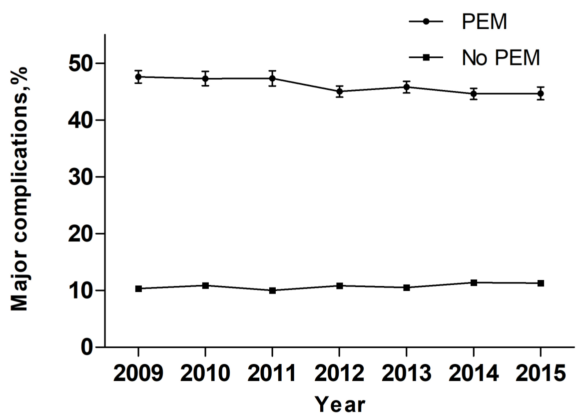


FIGURE 4
Major complications in patients with and without PEM between 2009 and 2015 in the United States.

4 Discussion

In the present study, we found the rate of PEM in patients underwent MSC was 7.1% by analyzing data of more than 1 million patients from NIS database. Patients with PEM were older, more likely to be female, higher percentage of black subjects, a lower income, lower proportion of elective admission and higher proportion of operations for GI cancers. The EAPC of PEM was +7.17%. PEM patients had higher risk of mortality and major complications, as well as higher total cost and longer LOS when compared with non-PEM patients after MCS. PEM patients who underwent lung resection and colectomy had the highest mortality rate while PEM significantly increased the risk of mortality and major complications in those underwent prostatectomy, hysterectomy and lung resection.

PEM is a common problem in cancer patients and has been recognized as a poor prognostic factor of postoperative complications and death (23). In the past decade, early identification and prevention of PEM have attracted increasing attention, many screening tools for malnutrition and guidelines for clinical nutrition in cancer have been advanced (24). In the present study, we reported that the prevalence of PEM in patients undergoing MCS was 7.1% (Table 1), which is much lower than other reports to focus on the prevalence of malnutrition in patients with cancer (20-70%) (8). The inconsistency of PEM prevalence was contributing to difference of cancer stage, cancer type and patient age (25). It is reported that the prevalence of moderate and severe malnutrition in stage III and IV patients was 79%, which is significantly higher than in stage I and II patients (3%) (26). Since relatively early-stage cancers are indicated for surgery, the impact of cancer on nutrition for those who undergo MCS is less than those in the late stages of cancer. Our study also indicated that subjects with relative early-stage cancer and PEM were more likely to be older, female, black, have low incomes, receive the operation in rural, urban non-teaching hospitals and lower-volume centers, and have more comorbidities, and were less likely on private insurance (Table 1). The difference in PEM rates among patients with different races, income statuses, properties and regions of hospitals, and types of insurance may be attributable to socioeconomic factors. Concerning female PEM patients, accumulating evidence suggests that vitamin disbalance play an important role in women's health and nutraceutical supplementation is an effective way to improve the situation (27, 28). Our results highlight the importance of targeting such groups who are susceptible to malnutrition and may lack nutrition support.

As cancer-related malnutrition is still largely unidentified, underestimated, and undertreated in clinical practice, many screening tools have been recommended. Groups including the European Society for Clinical Nutrition and Metabolism and the American Cancer Society have been developing guidelines regarding nutrition in cancer patients (29, 30). Our study revealed that the prevalence of PEM among patients for MCS was continuously risen. As the importance of assessing nutritional status before cancer surgery has gained more notice by surgeons, there is reason to believe that the increasing prevalence of PEM is owing to improvements in its detection rate. Meanwhile, the mortality rate in both the PEM and non-PEM groups decreased from 2009 to 2015, and the EAPC of mortality was -4.52 and -4.21%, respectively, which implies the rate of mortality decrease seen in the PEM group exceeds that of the non-PEM group. Notably, other studies have also shown a decreasing trend in mortality after MCS from 1999 to 2009, with a reported EAPC of -2.4%. During the same period, the overall

TABLE 2 Comparison of clinical outcomes following major cancer surgery in patients with and without PEM.

Outcomes	Event rates (%)		Adjusted OR (95%CI)#	P-value
	With PEM	Without PEM		
Mortality	1491(7.77)	2960(1.19)	2.26(2.08,2.44)	<0.0001
Major complications	8850(46.09)	26671(10.69)	2.46(2.36,2.56)	<0.0001
Pneumonia	4155(21.64)	11307(4.53)	2.52(2.40,2.65)	<0.0001
Pulmonary embolism	541(2.82)	1523(0.61)	1.62(1.44,1.82)	<0.0001
Renal failure	4398(22.91)	12131(4.86)	1.98(1.89,2.07)	<0.0001
Acute ischemic stroke	246(1.28)	662(0.27)	1.98(1.68,2.33)	<0.0001
Acute myocardial infarction	446(2.32)	1482(0.59)	1.44(1.28,1.62)	<0.0001
Cardiac arrest	283(1.47)	822(0.33)	1.88(1.61,2.20)	<0.0001
Adult respiratory distress syndrome	2733(14.23)	5784(2.32)	2.51(2.36,2.68)	<0.0001
Sepsis	1272(6.62)	1895(0.76)	3.08(2.82,3.36)	<0.0001
Septic shock	2002(10.43)	2590(1.04)	3.55(3.28,3.86)	<0.0001
Mechanical Ventilation	3698(19.26)	8125(3.26)	2.62(2.47,2.77)	<0.0001
Total cost, median (IQR)	35814(22292, 59579)	16825(11393, 24164)	0.39	<0.0001
Length of stay, median (IQR)	14(9,21)	4(2,7)	0.44	<0.0001

PEM, protein-energy malnutrition; IQR, interquartile range; OR, odds ratio; CI, confidence interval.
#Adjusted for age, sex, race, type of insurance, elective status, income quartile, hospital type, hospital region, hospital bed size, Elixhauser comorbidity index and surgical type.

mortality in all patients undergoing MCS was 2% (31). This study extends this knowledge. Meanwhile, a declining EAPC of major complications is only seen in the PEM group (-1.21%, 95% CI [-1.85–0.56], P < 0.01). This suggests that improved methods for the identification, prevention, and treatment of malnutrition in cancer patients have already made some difference.

Despite great advances in surgical techniques, postoperative recovery of cancer patients is tortuous, where malnutrition plays a major role (32). Our nationwide data analysis revealed that patients with PEM had a 2.26-fold risk of mortality compared to those without PEM after MCS, which was consistent with previous studies focusing on one specific cancer. Data analysis based on American College of Surgeons-National Surgical Quality Improvement Program from 2009 to 2013 indicated that patients with mild hypoalbuminemia, an indicator for malnutrition, had significantly higher postoperative mortality rates of colorectal cancer than those with normal albumin levels (OR=1.74; P < 0.001) (33). Furthermore, we made subgroup analysis to explore the influence of surgical type on mortality of PEM patients. Noteworthily, PEM patients had significantly high risk of mortality when undergoing non-GI surgery, including prostatectomy, hysterectomy and lung resection (Table 3). It is reasonable that malnutrition is more common in patients with GI cancers due to GI side effects of nausea, vomiting, anorexia, diarrhea, dysphagia, and malabsorption (34). However, once PEM occurs in patients with non-GI cancers, it always means that the patient's physical condition is very poor; therefore, the impact of PEM may be more pronounced in

TABLE 3 Subgroup analysis according to cancer surgical type.

Surgical type	Mortality	Major complications	Total cost	LOS
	OR(95%CI)#	OR(95%CI)#	Coefficient#	Coefficient#
Colectomy	2.05(1.86,2.26)	2.34(2.22,2.46)	0.39	0.38
Cystectomy	2.08(1.46,2.97)	3.04(2.64,3.51)	0.41	0.56
Esophagectomy	1.48(0.98,2.22)	1.86(1.52,2.27)	0.25	0.29
Gastrectomy	1.83(1.42,2.37)	2.01(1.77,2.28)	0.29	0.32
Hysterectomy	9.81(6.05,15.93)	5.38(4.36,6.63)	0.74	1.16
Lung resection	4.64(3.89,5.53)	3.49(3.17,3.84)	0.51	0.59
Pancreatectomy	1.51(1.21,1.87)	1.96(1.76,2.19)	0.29	0.37
Prostatectomy	13.59(3.26,56.65)	7.34(5.18,10.38)	0.65	1.14

OR, odds ratio; LOS, length of stay; CI, confidence interval.
#Adjusted for age, sex, race, type of insurance, elective status, income quartile, hospital type, hospital region, hospital bed size and Elixhauser comorbidity index.

such cases. Besides, it is reported that prostate cancers and cancers involving uterine corpus are generally diagnosed at lower stages and grades. In contrast, esophageal cancer and pancreatic cancer are generally diagnosed at later stages and are related to lower survival rates (4), which might also partially explain the strong effects of PEM on prostatectomy and hysterectomy as well as its relatively weak effects on esophagectomy and pancreatectomy. This suggests more attention should be paid to non-GI cancer patients with PEM whose nutritional statuses are always less noticed than GI cancer patients. Urgent and appropriate nutritional supplements should be administered to patients with PEM, thereby correcting PEM and improving their prognosis.

Apart from mortality, major complications play the key roles in perioperative recovery, hospital stay and total cost of cancer patients (35). Our study indicated that patients with PEM have a 2.46-fold increased risk of overall major complications compared to those without PEM after MCS (Table 2). It is worth noting that the highest OR related to PEM was sepsis (OR=3.08) and septic shock (OR=3.55), which was consistent with previous report (1). Cancer patients are considered to have baseline immunosuppression (36), and PEM worsens this condition, which inclines patients to immunologic deficiency due to protein deficiency and lack of immune mediators and consequently predisposes patients to susceptibility to infection (37). Sepsis always results in massive catabolism, characterized by the depletion of protein, fat, and glycogen energy reserves. It is common for patients with sepsis to experience muscle wasting and weight loss, which further causes or worsens malnutrition (38). Therefore, early screening of PEM and monitoring for infection symptoms, signs, and laboratory findings are crucial for cancer patients undergoing surgery. Furthermore, there was a higher risk of pneumonia (OR=2.52), adult respiratory distress syndrome (2.51), and mechanical ventilation (OR=2.62) in patients with PEM after MCS, which were resulted mainly from PEM-induced muscle weakness and PEM-related immunologic deficiency (39, 40). Also, higher risk of cardiac complications (acute myocardial infarction, cardiac arrest) were also observed from our study, which may result from high levels of inflammation and the progression of atherosclerosis (41) as well as cardiac structural alterations and the occurrence of heart failure (42).

There are several limitations of our study. First, the use of ICD-9-CM codes to identify these procedures and events relies largely on coding accuracy, which could be assigned erroneously. As PEM has not been rigorously validated in the NIS, if the misclassification occurs, it is impossible to access individual patient charts to confirm the diagnosis, which inevitably results in bias. Second, the NIS data set does not provide information for tumor stage and grade, laboratory values, or other cancer-related treatment received by the patients, which made it impossible to evaluating these parameters on outcomes. Third, the NIS data does not provide consistent surgeon identification, and there is a possible relationship between outcomes after MCS and the experience and practice patterns of surgeons or institutions. Fourth, as the information after discharge is not available from the NIS, the post-discharge outcomes could not be evaluated. Fifth, since the heterogenous patients and the restrictions of NIS database, it is not possible to extrapolate the information for each single cancer surgery. Despite these shortcomings, the NIS is a large and reliable database containing hospitalized patient data from over 4,000 hospitals in over 30 states in the United States, and temporal trend analyses are performed during a 6-year time span, which affords more power to the study. Moreover, the database has been widely applied in other retrospective studies. In addition, the impact of PEM on outcomes is independent of confounding variables in the multivariable and double robust inverse probability of treatment weighting method. Also, we investigate the influence of surgical type on perioperative outcomes, aiming to provide more comprehensive information concerning surgical type and relating outcome. Since the present study was observational, prospective studies are needed to verify the impact of PEM on worse outcomes after MCS.

In conclusion, we found PEM had severe impact on mortality, major complications, total cost and LOS of cancer patients underwent MCS by analyzing data of more than one million patients. PEM patients who underwent lung resection and colectomy had the highest mortality rate while PEM significantly increased the risk of mortality and major complications in those underwent prostatectomy, hysterectomy and lung resection. Also, we discovered consistently increasing PEM rates and the conversely decreasing EAPC of both mortality and major complications in the PEM group undergoing MCS from 2009 to 2015, which are likely the result of improved screening tools, evolving guidelines, and better management. Prompt recognition of PEM and the initiation of appropriate nutrition therapy is essential to achieve better outcomes after MCS.

Data availability statement

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

Author contributions

JJ, XZ, ZD, YL, and HL designed research. JJ, XZ, PZ, and YX conducted research. JJ, ZD, and HH analyzed data. JJ, XZ, YL, and HL wrote the paper. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Key R&D Program of China (2018YFC1314100), the Key-Area Research and Development Program of Guangdong Province (2019B020230001), the National Natural Science Foundation of China Youth Science Foundation (82201551), the Natural Science Foundation of Guangdong Province (2022A1515011306, 2020A1515010268, 2020A1515010049, 2019A1515010275), the Outstanding Young Talents Foundation of Guangdong Provincial People's Hospital (KJ012019091), the Program of Science and Technology of Guangzhou (202103020166, 201904010424), NSFC Incubation Project of Guangdong Provincial People's Hospital(KY0120220031), the Fundamental Research Funds for the Central Universities(2020ZYGXZR010).

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.970187/full#supplementary-material

References

1. Adejumo AC, Akanbi O, Pani L. Protein energy malnutrition is associated with worse outcomes in sepsis-a nationwide analysis. *J Acad Nutr Dietetics* (2019) 119 (12):2069–84. doi: 10.1016/j.jand.2019.04.019

2. Adejumo AC, Adejumo KL, Adegbala OM, Enwerem N, Ofosu A, Akanbi O, et al. Inferior outcomes of patients with acute myocardial infarction and comorbid protein-energy malnutrition. *JPEN J parenteral enteral Nutr* (2020) 44(3):454–62. doi: 10.1002/jpen.1680

3. Adejumo AC, Adejumo KL, Adegbala OM, Chinedozi I, Ndansi J, Akanbi O, et al. Protein-energy malnutrition and outcomes of hospitalizations for heart failure in the USA. *Am J Cardiol* (2019) 123(6):929–35. doi: 10.1016/j.amjcard.2018.12.014

4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654

5. Jiang D, Zhang L, Liu W, Ding Y, Yin J, Ren R, et al. Trends in cancer mortality in China from 2004 to 2018: A nationwide longitudinal study. *Cancer Commun (London England).* (2021) 41(10):1024–36. doi: 10.1002/cac2.12195

6. Laganà AS, Vitale SG, Nigro A, Sofo V, Salmeri FM, Rossetti P, et al. Pleiotropic actions of peroxisome proliferator-activated receptors (PPARs) in dysregulated metabolic homeostasis, inflammation and cancer: Current evidence and future perspectives. *Int J Mol Sci* (2016) 17(7):999. doi: 10.3390/ijms17070999

7. Vitale SG, Laganà AS, Nigro A, La Rosa VL, Rossetti P, Rapisarda AM, et al. Peroxisome proliferator-activated receptor modulation during metabolic diseases and cancers: Master and minions. *PPAR Res* (2016) 2016:6517313. doi: 10.1155/2016/6517313

8. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr (Edinburgh Scotland).* (2017) 36(5):1187–96. doi: 10.1016/j.clnu.2017.06.017

9. Lakananurak N, Gramlich L. The role of preoperative parenteral nutrition. *Nutrients* (2020) 12(5):1320. doi: 10.3390/nu12051320

10. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Maeda S, Haraguchi N, et al. Prevalence of malnutrition among gastric cancer patients undergoing gastrectomy and optimal preoperative nutritional support for preventing surgical site infections. *Ann Surg Oncol* (2015) 22 Suppl 3:S778–85. doi: 10.1245/s10434-015-4820-9

11. Lee DU, Fan GH, Hastie DJ, Addonizio EA, Suh J, Prakasam VN, et al. The clinical impact of malnutrition on the postoperative outcomes of patients undergoing colorectal resection surgery for colon or rectal cancer: Propensity score matched analysis of 2011-2017 US hospitals. *Surg Oncol* (2021) 38:101587. doi: 10.1016/j.suronc.2021.101587

12. Fukami Y, Saito T, Arikawa T, Osawa T, Komatsu S, Kaneko K, et al. European Society for clinical nutrition and metabolism (ESPEN) malnutrition criteria for predicting major complications after hepatectomy and pancreatectomy. *World J Surg* (2021) 45 (1):243–51. doi: 10.1007/s00268-020-05767-w

13. Bagan P, Berna P, De Dominicis F, Das Neves Pereira JC, Mordant P, de la Tour B, et al. Nutritional status and postoperative outcome after pneumonectomy for lung cancer. *Ann Thorac Surg* (2013) 95(2):392–6. doi: 10.1016/j.athoracsur.2012.06.023

14. Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. *Nat Rev Clin Oncol* (2016) 13(3):185–98. doi: 10.1038/nrclinonc.2015.200

15. Tobert CM, Hamilton-Reeves JM, Norian LA, Hung C, Brooks NA, Holzbeierlein JM, et al. Emerging impact of malnutrition on surgical patients: Literature review and potential implications for cystectomy in bladder cancer. *J Urol* (2017) 198(3):511–9. doi: 10.1016/j.juro.2017.01.087

16. Soloff MA, Vargas MV, Wei C, Ohnona A, Tyan P, Gu A, et al. Malnutrition is associated with poor postoperative outcomes following laparoscopic hysterectomy. *JSLS* (2021) 25(1):e2020.00084. doi: 10.4293/JSLS.2020.00084

17. Tan HJ, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of geriatric events among older adults undergoing major cancer surgery. *J Clin Oncol Off J Am Soc Clin Oncol* (2016) 34(11):1231–8. doi: 10.1200/JCO.2015.63.4592

18. Sammon J, Trinh VQ, Ravi P, Sukumar S, Gervais MK, Shariat SF, et al. Health care-associated infections after major cancer surgery: temporal trends, patterns of care, and effect on mortality. *Cancer* (2013) 119(12):2317–24. doi: 10.1002/cncr.28027

19. Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflammatory bowel diseases.* (2008) 14(8):1105–11. doi: 10.1002/ibd.20429

20. Burke LG, Frakt AB, Khullar D, Orav EJ, Jha AK. Association between teaching status and mortality in US hospitals. *Jama* (2017) 317(20):2105–13. doi: 10.1001/jama.2017.5702

21. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* (1998) 36(1):8–27. doi: 10.1097/00005650-199801000-00004

22. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* (2015) 34(28):3661–79. doi: 10.1002/sim.6607

23. McKenna NP, Bews KA, Al-Refaie WB, Colibaseanu DT, Pemberton JH, Cima RR, et al. Assessing malnutrition before major oncologic surgery: One size does not fit all. *J Am Coll Surgeons.* (2020) 230(4):451–60. doi: 10.1016/j.jamcollsurg.2019.12.034

24. Reber E, Schönenberger KA, Vasiloglou MF, Stanga Z. Nutritional risk screening in cancer patients: The first step toward better clinical outcome. *Front Nutr* (2021) 8:603936. doi: 10.3389/fnut.2021.603936

25. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J parenteral enteral Nutr* (2014) 38(2):196–204. doi: 10.1177/0148607113502674

26. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol (Royal Coll Radiologists (Great Britain)).* (2003) 15(8):443–50. doi: 10.1016/S0936-6555(03)00155-9

27. Rizzo G, Laganà AS, Rapisarda AM, La Ferrera GM, Buscema M, Rossetti P, et al. Vitamin B12 among vegetarians: Status, assessment and supplementation. *Nutrients* (2016) 8(12):767. doi: 10.3390/nu8120767

28. Paul C, Laganà AS, Maniglio P, Triolo O, Brady DM. Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives. *Gynecological Endocrinol Off J Int Soc Gynecological Endocrinol* (2016) 32(6):431–8. doi: 10.3109/09513590.2016.1144741

29. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al. American Cancer society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA: Cancer J Clin* (2012) 62(1):30–67. doi: 10.3322/caac.20140

30. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: Clinical nutrition in cancer. *Clin Nutr (Edinburgh Scotland).* (2021) 40(5):2898–913. doi: 10.1016/j.clnu.2021.02.005

31. Trinh VQ, Karakiewicz PI, Sammon J, Sun M, Sukumar S, Gervais MK, et al. Venous thromboembolism after major cancer surgery: temporal trends and patterns of care. *JAMA Surg* (2014) 149(1):43–9. doi: 10.1001/jamasurg.2013.3172

32. Martínez-Ortega AJ, Piñar-Gutiérrez A, Serrano-Aguayo P, González-Navarro I, Remón-Ruíz PJ, Pereira-Cunill JL, et al. Perioperative nutritional support: A review of current literature. *Nutrients* (2022) 14(8):1601. doi: 10.3390/nu14081601

33. Hu WH, Eisenstein S, Parry L, Ramamoorthy S. Preoperative malnutrition with mild hypoalbuminemia associated with postoperative mortality and morbidity of colorectal cancer: a propensity score matching study. *Nutr J* (2019) 18(1):33. doi: 10.1186/s12937-019-0458-y

34. Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *J Hum Nutr dietetics Off J Br Dietetic Assoc* (2010) 23(4):393–401. doi: 10.1111/j.1365-277X.2010.01058.x

35. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clin Nutr (Edinburgh Scotland).* (2021) 40(7):4745–61. doi: 10.1016/j.clnu.2021.03.031

36. Sammon JD, Klett DE, Sood A, Olugbade KJr., Schmid M, Kim SP, et al. Sepsis after major cancer surgery. *J Surg Res* (2015) 193(2):788–94. doi: 10.1016/j.jss.2014.07.046

37. Batool R, Butt MS, Sultan MT, Saeed F, Naz R. Protein-energy malnutrition: a risk factor for various ailments. *Crit Rev Food Sci Nutr* (2015) 55(2):242–53. doi: 10.1080/10408398.2011.651543

38. Wischmeyer PE. Nutrition therapy in sepsis. *Crit Care clinics.* (2018) 34(1):107–25. doi: 10.1016/j.ccc.2017.08.008

39. Baba H, Tokai R, Hirano K, Watanabe T, Shibuya K, Hashimoto I, et al. Risk factors for postoperative pneumonia after general and digestive surgery: a retrospective single-center study. *Surg Today* (2020) 50(5):460–8. doi: 10.1007/s00595-019-01911-9

40. Howes N, Atkinson C, Thomas S, Lewis SJ. Immunonutrition for patients undergoing surgery for head and neck cancer. *Cochrane Database systematic Rev* (2018) 8(8):Cd010954. doi: 10.1002/14651858.CD010954.pub2

41. Raposeiras Roubín S, Abu Assi E, Cespón Fernandez M, Barreiro Pardal C, Lizancos Castro A, Parada JA, et al. Prevalence and prognostic significance of malnutrition in patients with acute coronary syndrome. *J Am Coll Cardiol* (2020) 76 (7):828–40. doi: 10.1016/j.jacc.2020.06.058

42. Kalla A, Krishnamoorthy P, Gopalakrishnan A, Garg J, Patel NC, Figueredo VM. Gender and age differences in cardiovascular complications in anorexia nervosa patients. *Int J Cardiol* (2017) 227:55–7. doi: 10.1016/j.ijcard.2016.11.209

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 01 March 2023
DOI 10.3389/fonc.2023.1083618

Check for updates

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Maolan Li,
Shanghai Jiao Tong University, China
Marco Massani,
ULSS2 Marca Trevigiana, Italy
Luca Saadeh,
University Hospital of Padua, Italy

*CORRESPONDENCE
Qilong Duan
Duanqilongsdmc@126.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 29 October 2022
ACCEPTED 17 February 2023
PUBLISHED 01 March 2023

CITATION
Xu X, Wang J and Duan Q (2023) Effects of surgery on survival of elderly patients with gallbladder cancer: A propensity score matching analysis of the SEER database. *Front. Oncol.* 13:1083618.
doi: 10.3389/fonc.2023.1083618

Effects of surgery on survival of elderly patients with gallbladder cancer: A propensity score matching analysis of the SEER database

Xiaoming Xu[1†], Jingzhi Wang[2†] and Qilong Duan[3*]

[1]Department of Gastroenterology, Jining First People's Hospital, Jining, China, [2]Department of Radiotherapy Oncology, The Affiliated Yancheng First Hospital of Nanjing University Medical School, The First People's Hospital of Yancheng, Yancheng, China, [3]Shandong Medical College, Jinan, China

Background: Surgery is the sole curative therapy for gallbladder cancer (GBC) patients. Confronting an aging society, the demand to treat elderly patients with GBC is increasing. But there are few reports on survival benefit in elderly GBC patients treated with surgery. Therefore, we designed this population-based study to assess the survival benefit of surgery in GBC patients aged 70 years or older.

Methods: GBC patients aged 70 years or older were identified in the surveillance, epidemiology, and end results cancer (SEER) database from 2010 to 2017. A 1:1 propensity score matching (PSM) analysis was conducted to balance the baseline data of patients. Overall survival (OS) and cancer-specific survival (CSS) of patients were evaluated by Kaplan-Meier analysis and compared with log-rank test. Independent risk factors associated with OS and CSS were determined by univariate and multivariate Cox proportional hazard regression analyses and subgroup analysis were performed.

Results: A total of 2055 GBC patients aged 70 years or older were included in our study, with 1734 patients underwent surgery. Before PSM, the age, AJCC stage, TNM stage, and chemotherapy were significantly different between the surgery and no-surgery group (all $P<0.05$). Patients with surgery had significantly longer OS and CSS than those without surgery ($P<0.0001$). After 1:1 PSM, the differences in clinicopathological characteristics were reduced (all $P>0.05$). Kaplan-Meier analysis also showed patients received surgery had significantly better OS and CSS ($P<0.0001$). Subgroup analysis further indicated that almost all subgroups received surgery had OS and CSS advantage, especially patients aged 70-84 years old. Finally, univariate and multivariate COX regression analyses showed that age, AJCC stage and T stage were independent prognostic factors for OS and CSS in patients undergoing surgery.

Conclusion: Our study found that surgery significantly improved OS and CSS in GBC patients aged 70-84 years, but more prospective studies are needed to prove our findings.

KEYWORDS

PSM, old age, SEER database, OS, CSS, gallbladder cancer

1 Introduction

Gallbladder cancer (GBC) is a rare tumor ranking sixth among most common gastrointestinal cancer, and the most prevalent cancer of biliary tract (1, 2). The estimated number of new GBC cases was 115,949, representing 0.6% of all cancer cases in 2020 (3). It is well known that gallbladder adenocarcinoma (GBAC) is the most common pathological type of gallbladder cancer. The elderly patients account for the vast majority of patients with gallbladder cancer, previous study showed that the median age of GBC patients was 71 years (4). The prognosis of patients with gallbladder cancer deteriorates with age, the increasing incidence and mortality rates were primarily observed in men≥60 years and in women≥70 years of age (5). Surgery is the first line of treatment for gallbladder cancer patients (6). Currently, there have not been standard treatment guidelines for GBC in the elderly patients. Treatment in these patients remains a complicated issue because of the limited evidence, pre-existing disease, and adverse drug reactions, which lead to either undertreatment or overtreatment. Study demonstrated that complication rates, length of hospital stay, and intensive care unit admissions increased with patient age (7). The benefit of surgery for the old population has been discussed, but the results were contradictory (8–10). Several studies have also shown that age is a risk factor for prognosis in patients undergoing surgery for gallbladder cancer (11, 12). Thus, whether elderly patients with gallbladder cancer can benefit from surgical treatment or not is a topic worth exploring.

Therefore, in the current study, we extracted data of elderly patients with gallbladder cancer from the Surveillance, Epidemiology, and End Results (SEER) database, in order to clarify the impact of surgery on elderly GBC patients (≥70 years old).

2 Materials and methods

2.1 Patient selection

The patient data were obtained from the SEER database, which is openly accessible and freely available for researchers. We used the SEER*Stat software with a data user agreement, the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) Code C23.9 was used as a reference for selection. The inclusion criteria were as follows: Patients diagnosed with GBC between 2010-2017. The diagnosis was confirmed by positive histology, and the type of reporting source was not autopsy or death certificate. Patients diagnosed as non-adenocarcinoma, younger than 70 years old, survival time less than 1 month, lacking data about pathological diagnosis, TNM stage and survival were excluded. The data for patients' sex, age, marital status, race, AJCC stage, TNM stage, surgery status, radiation status and chemotherapy status were identified. Our detailed workflow was shown in Figure 1.

2.2 Statistical analysis

Clinicopathological characteristics were compared between surgery and no-surgery group by Chi-square and Fisher's exact probability tests. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death due to any cause or the last follow-up. Cancer cause-specific survival (CSS) was defined as the time from the date of diagnosis to the date of death from cancer. Univariate and multivariate Cox proportional risk regression analyses were applied to identifying independent risk factors on survival of GBC patients. Survival analysis was accomplished by the Kaplan-Meier method and the log-rank test. Propensity score matching (PSM) was conducted to calibrate the effects of the baseline data differences. All the statistical analyses and graphics were performed with the R statistical software.

3 Results

3.1 Characteristics of patients

Among 8583 GBC patients originally identified from SEER database, cases of 1734 patients treated with surgery and 321 without surgery from 2010 to 2017 were included in our study. The clinicopathological characteristics between two groups before PSM were summarized in Table 1. A majority were female in both surgery and no-surgery group (67.99% vs 69.78%, P=0.571), and most of them were White (80.22% vs 76.95%, P=0.237). The proportion of patients aged 75-85 years was higher in surgery group compared with no-surgery group (72.43% vs 63.24%, P=0.005). In total, 18.4% of the patients with surgery versus 72.59% of those without surgery were AJCCIV(P<0.001). Compared with patients underwent surgery, significantly more

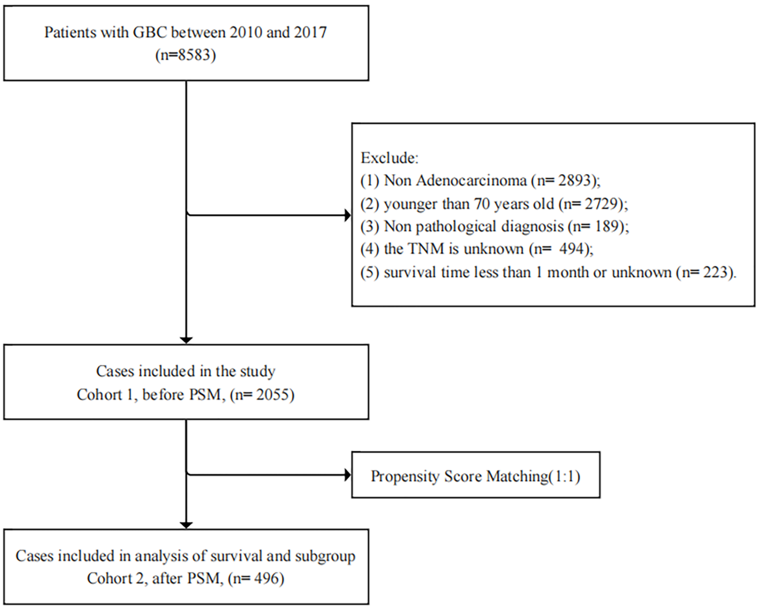


FIGURE 1
Enrollment flow chart of eligible patients in the present study.

patients in no-surgery group had TNM clinical stage of T4 (12.46% vs 1.85%, P < 0.001), N2 (9.97% vs 2.77%, P < 0.001), and M1 (64.80% vs 15.80%, P < 0.001). The PSM method was used to balance all characteristics, including sex, age, marital status, race, AJCC, TNM stage, chemotherapy, radiotherapy, and chemotherapy between surgery and no-surgery groups. And a total of 248 surgery patients were matched with 248 no-surgery patients (1:1). The clinicopathological characteristics were shown in Table 2. Most of the patients were female in both surgery and no-surgery group (68.15% vs 70.97%, P= 0.558). Approximately 62% patients were aged 70-79 years in both two groups (P=0.146). AJCCIVtumors (65.73% vs 64.52%, P = 0.565) as well as TNM clinical stage of T4 (7.66% vs 6.45%, P < 0.726), N2 (9.27% vs 8.06%, P < 0.213), and M1 (56.45% vs 57.26%, P=0.928) were balanced in two groups.

TABLE 1 Clinical characteristics of elderly patients with GBC before propensity score matching.

Characters	No surgery (n=321)	Surgery (n=1734)	p value
Sex			0.571
Male	97 (30.22)	555 (32.01)	
Female	224 (69.78)	1179 (67.99)	
Age			0.005
70-74	118 (36.76)	478 (27.57)	
75-79	84 (26.17)	461 (26.59)	
80-84	69 (21.50)	435 (25.09)	
≥85	50 (15.58)	360 (20.76)	
Marital			0.191
No	165 (51.40)	963 (55.54)	
Married	156 (48.60)	771 (44.46)	
Race			0.237
White	247 (76.95)	1391 (80.22)	
Black	39 (12.15)	159 (9.17)	
Other	35 (10.90)	184 (10.61)	

(Continued)

TABLE 1 Continued

Characters	No surgery (n=321)	Surgery (n=1734)	p value
AJCC			<0.001
I	6 (1.87)	222 (12.80)	
II	1 (0.31)	636 (36.68)	
III	81 (25.23)	557 (32.12)	
IV	233 (72.59)	319 (18.40)	
T			<0.001
T1	41 (12.77)	244 (14.07)	
T2	7 (2.18)	898 (51.79)	
T3	233 (72.59)	560 (32.30)	
T4	40 (12.46)	32 (1.85)	
N			<0.001
N0	199 (61.99)	1313 (75.72)	
N1	90 (28.04)	373 (21.51)	
N2	32 (9.97)	48 (2.77)	
M			<0.001
M0	113 (35.20)	1460 (84.20)	
M1	208 (64.80)	274 (15.80)	
Radiation			0.503
No/Unknown	282 (87.85)	1496 (86.27)	
Yes	39 (12.15)	238 (13.73)	
Chemotherapy			<0.001
No/Unknown	147 (45.79)	1262 (72.78)	
Yes	174 (54.21)	472 (27.22)	
months	4.00 (2.00, 10.00)	17.00 (6.00, 38.00)	<0.001

TABLE 2 Clinical characteristics of elderly patients with GBC after propensity score matching.

Characters	No surgery (n=248)	Surgery (n=248)	p value
Sex			0.558
Male	72 (29.03)	79 (31.85)	
Female	176 (70.97)	169 (68.15)	
Age			0.146
70-74	79 (31.85)	78 (31.45)	
75-79	75 (30.24)	76 (30.65)	
80-84	55 (22.18)	70 (28.23)	
≥85	39 (15.73)	24 (9.68)	
Marital			0.999
No	131 (52.82)	131 (52.82)	

(Continued)

TABLE 2 Continued

Characters	No surgery (n=248)	Surgery (n=248)	p value
Married	117 (47.18)	117 (47.18)	
Race			0.749
White	192 (77.42)	192 (77.42)	
Black	27 (10.89)	23 (9.27)	
Other	29 (11.69)	33 (13.31)	
AJCC			0.565
I	6 (2.42)	2 (0.81)	
II	1 (0.40)	1 (0.40)	
III	81 (32.66)	82 (33.06)	
IV	160 (64.52)	163 (65.73)	
T			0.726
T1	20 (8.06)	18 (7.26)	
T2	7 (2.82)	11 (4.44)	
T3	205 (82.66)	200 (80.65)	
T4	16 (6.45)	19 (7.66)	
N			0.213
N0	160 (64.52)	141 (56.85)	
N1	68 (27.42)	84 (33.87)	
N2	20 (8.06)	23 (9.27)	
M			0.928
M0	106 (42.74)	108 (43.55)	
M1	142 (57.26)	140 (56.45)	
Radiation			0.234
No/Unknown	220 (88.71)	210 (84.68)	
Yes	28 (11.29)	38 (15.32)	
Chemotherapy			0.928
No/Unknown	130 (52.42)	128 (51.61)	
Yes	118 (47.58)	120 (48.39)	
months	4.00 (2.00, 9.00)	8.00 (3.00, 18.00)	<0.001

Other characteristics, including marital status, race, radiotherapy, and chemotherapy status also showed no significantly difference between the two groups (all P>0.05).

3.2 Univariate and multivariate analysis after propensity score matching

We explored the potential independent prognosis factor for GBC patients through univariate and multivariate Cox regression analysis. Multivariate analysis showed that age≥85 years old (HR=1.661, 95%CI: 1.216-2.268, P=0.001), M1 (HR=1.774, 95% CI: 1.455-2.163, P<0.001) were significantly associated with poor OS. Surgery (HR=0.633, 95%CI: 0.527-0.761, P<0.001) and chemotherapy (HR=0.568, 95%CI: 0.466-0.694, P<0.001) were significantly associated with better OS (Table 3). The same results were also observed on the analysis of CSS. Age≥85 years old (HR=1.507, 95%CI: 1.076-2.111), M1 (HR=1.862, 95%CI: 1.504-2.306, P<0.001) were significantly associated with poor CSS. Surgery (HR=0.607, 95%CI: 0.498-0.739, P<0.001) and chemotherapy (HR=0.599, 95%CI: 0.484-0.741, P<0.001) were significantly associated with better CSS (Table 4).

TABLE 3 Univariate and multivariate Cox regression analysis of OS after propensity score matching.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Sex						
Male	1.000					
Female	1.018	0.836-1.238	0.862			
Age						
70-74	1.000			1.000		
75-79	1.122	0.891-1.413	0.327	0.998	0.791-1.261	0.990
80-84	0.962	0.754-1.229	0.758	0.892	0.691-1.151	0.379
≥85	2.219	1.643-2.996	<0.001	1.661	1.216-2.268	0.001
Marital						
No	1.000			1.000		
Married	0.805	0.671-0.966	0.019	0.926	0.767-1.117	0.421
Race						
White	1.000					
Black	1.044	0.770-1.416	0.779			
Other	0.958	0.730-1.257	0.757			
AJCC						
I	1.000					
II	1.070	0.222-5.163	0.933			
III	1.184	0.554-2.530	0.663			
IV	1.913	0.902-4.057	0.091			
T						
T1	1.000					
T2	0.982	0.551-1.749	0.951			
T3	1.284	0.911-1.808	0.153			
T4	1.071	0.665-1.725	0.777			
N						
N0	1.000					
N1	0.991	0.811-1.211	0.928			
N2	1.052	0.758-1.461	0.760			
M						
M0	1.000			1.000		
M1	1.699	1.408-2.048	<0.001	1.774	1.455-2.163	<0.001
Surgery						
No	1.000			1.000		
Yes	0.616	0.513-0.739	<0.001	0.633	0.527-0.761	<0.001
Radiation						
No/Unknown	1.000			1.000		

(Continued)

TABLE 3 Continued

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Yes	0.542	0.411-0.716	<0.001	0.791	0.590-1.061	0.118
Chemotherapy						
No/Unknown	1.000			1.000		
Yes	0.577	0.481-0.692	<0.001	0.568	0.466-0.694	<0.001

TABLE 4 Univariate and multivariate Cox regression analysis of CSS after propensity score matching.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Sex						
Male	1.000					
Female	1.060	0.857-1.310	0.590			
Age						
70-74	1.000			1.000		
75-79	1.081	0.844-1.384	0.539	0.970	0.755-1.245	0.808
80-84	0.966	0.745-1.253	0.794	0.905	0.69-1.187	0.469
≥85	2.036	1.471-2.817	<0.001	1.507	1.076-2.111	0.017
Marital						
No	1.000			1.000		
Married	0.733	0.602-0.892	0.002	0.837	0.684-1.023	0.083
Race						
White	1.000					
Black	1.111	0.810-1.523	0.514			
Other	0.837	0.616-1.138	0.257			
AJCC						
I	1.000					
II	0.710	0.083-6.088	0.755			
III	1.373	0.562-3.357	0.487			
IV	2.301	0.949-5.580	0.065			
T						
T1	1.000					
T2	0.968	0.513-1.827	0.920			
T3	1.347	0.926-1.958	0.119			
T4	1.042	0.616-1.762	0.877			
N						
N0	1.000					

(Continued)

TABLE 4 Continued

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
N1	0.933	0.751-1.160	0.535			
N2	1.045	0.737-1.482	0.804			
M						
M0	1.000			1.000		
M1	1.810	1.479-2.216	<0.001	1.862	1.504-2.306	<0.001
Surgery						
No	1.000			1.000		
Yes	0.596	0.490-0.726	<0.001	0.607	0.498-0.739	<0.001
Radiation						
No/Unknown	1.000			1.000		
Yes	0.514	0.378-0.698	<0.001	0.756	0.548-1.044	0.089
Chemotherapy						
No/Unknown	1.000			1.000		
Yes	0.604	0.497-0.734	<0.001	0.599	-0.484-0.741	<0.001

3.3 Survival analysis of surgery and no-surgery patients

Before PSM, patients in surgery group had significantly longer OS and CSS compared with patients in no-surgery group (median OS: 17 months vs 4 months, P < 0.001; median CSS: 26 months vs 5 months, P < 0.001, Figure 2). After adjusting for variables (sex, age, marital status, AJCC, TNM stage, radiotherapy and chemotherapy), surgery group still performed better OS and CSS (median OS: 8 months vs 4 months, P < 0.0001; median CSS: 9 months vs 5 months, P < 0.001, Figure 3).

3.4 Subgroup analysis of survival between surgery and no-surgery patients

Considering the reduction of selection bias, patients were stratified into subgroups according to the different clinical

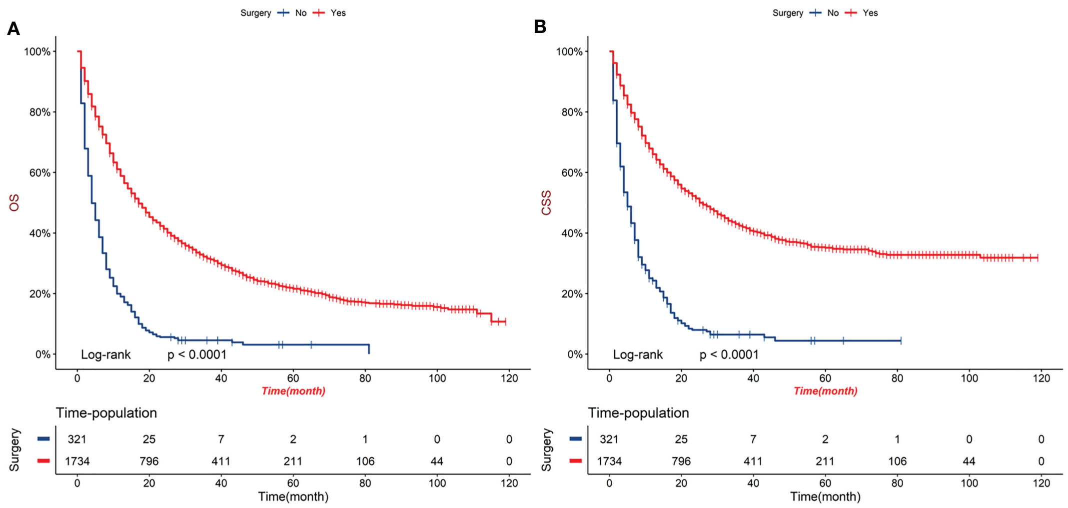


FIGURE 2
Kaplan-Meier curves of OS **(A)** and CSS **(B)** of order GBC patients before PSM.

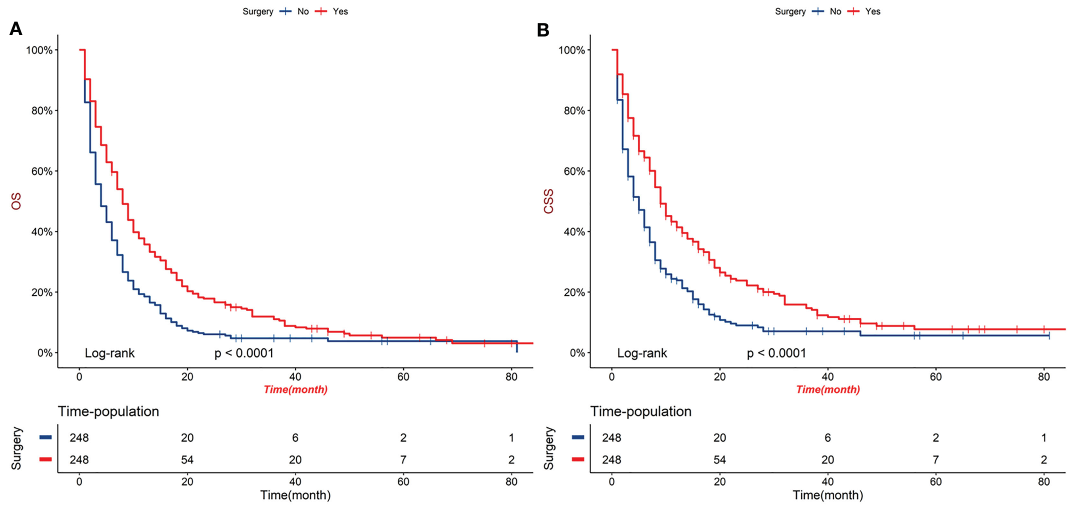


FIGURE 3
Kaplan-Meier curves of OS **(A)** and CSS **(B)** of order GBC patients after PSM.

characteristics, and subgroup analysis were performed (Figure 4). The results showed that surgery was a protective prognostic factor for OS in almost all subgroups, including patients aged 70-84 years old. AJCCIandIIsubgroups presented insignificant differences in OS between surgery and no-surgery patients because of a small number of available cases. The CSS subgroup analysis showed that surgical treatment was a protective factor for DSS survival in the same subgroups as OS.

3.5 Prognostic factors of patients undergoing surgery

To further investigate the prognostic factors affecting elderly patients who underwent surgery, we performed univariate and multivariate cox regression analyses. The results showed that age, AJCC stage and T stage were independent risk factors for OS (Table 5) and CSS (Table 6). In addition, marriage was also an independent risk factor for OS but not for CSS.

4 Discussion

Surgery remains a fundamental part of GBC management and is the only potentially curative modality (13). Although many studies have reported some prognostic factors for GBC patients, including age, TNM stage, tumor size, adjuvant therapy, and pathological grade (11, 14–17), there were little data on the survival benefit of surgery in elderly patients with GBC. This special population was rarely included in randomized controlled trials that exploring the effect of surgery. Only a few observational studies have investigated this problem, but the applicability of the results was limited by the

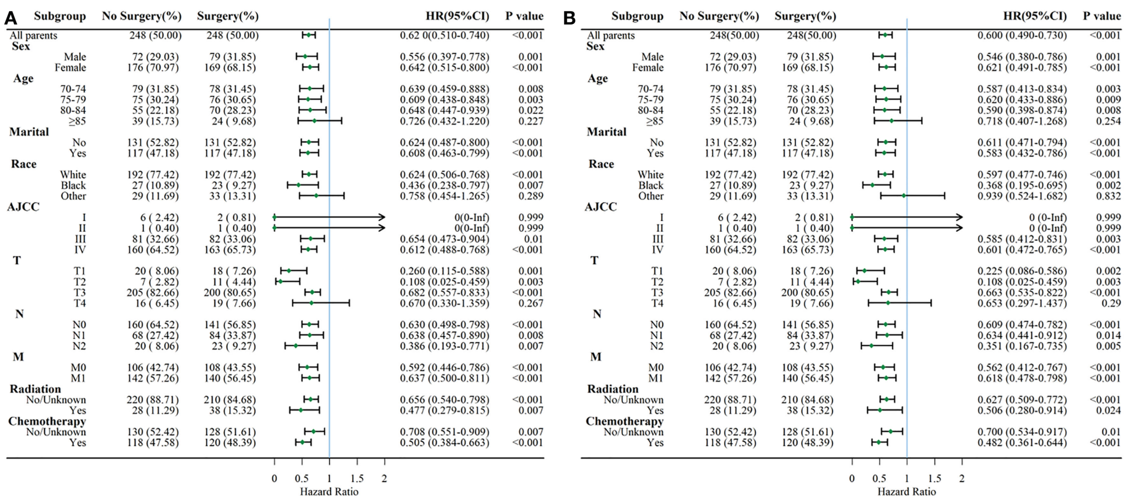


FIGURE 4
Subgroup analysis comparing OS **(A)** and CSS **(B)** between surgery and no-surgery order GBC patients.

TABLE 5 Univariate and multivariate Cox regression analysis of OS for patients underwent surgery.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Sex						
Male	1.000					
Female	1.035	0.923-1.161	0.557			
Age						
70-74	1.000			1.000		
75-79	1.187	1.021-1.381	0.025	1.253	1.077-1.458	0.004
80-84	1.315	1.131-1.528	0.000	1.412	1.212-1.646	0.000
≥85	1.621	1.386-1.896	0.000	1.963	1.668-2.311	0.000
Marital						
No	1.000			1.000		
Married	0.848	0.761-0.945	0.003	0.892	0.797-0.998	0.046
Race						
White	1.000					
Black	0.885	0.729-1.075	0.219			
Other	0.922	0.772-1.1	0.366			
AJCC						
I	1.000			1.000		
II	1.222	1.005-1.487	0.045	0.959	0.568-1.619	0.875
III	2.436	2.006-2.959	0.000	1.396	0.837-2.328	0.202
IV	4.820	3.91-5.941	0.000	2.785	1.377-5.63	0.004
T						
T1	1.000			1.000		
T2	1.338	1.12-1.6	0.001	1.279	0.787-2.079	0.321
T3	3.266	2.716-3.927	0.000	2.240	1.393-3.602	0.001
T4	3.954	2.668-5.861	0.000	1.467	0.767-2.807	0.247
N						
N0	1.000			1.000		
N1	1.404	1.236-1.596	0.000	0.973	0.828-1.145	0.744
N2	2.157	1.588-2.931	0.000	0.879	0.568-1.36	0.562
M						
M0	1.000			1.000		
M1	3.123	2.716-3.59	0.000	1.238	0.757-2.023	0.395
Radiation						
No/Unknown	1.000					
Yes	0.857	0.733-1.001	0.052			
Chemotherapy						
No/Unknown	1.000					
Yes	0.945	0.838-1.066	0.356			

10.3389/fonc.2023.1083618

TABLE 6 Univariate and multivariate Cox regression analysis of CSS for patients underwent surgery.

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Sex						
Male	1.000					
Female	1.002	0.876-1.147	0.974			
Age						
70-74	1.000			1.000		
75-79	1.181	0.995-1.402	0.056	1.251	1.053-1.486	0.011
80-84	1.135	0.952-1.354	0.158	1.246	1.042-1.489	0.016
≥85	1.256	1.04-1.516	0.018	1.654	1.365-2.004	0.000
Marital						
No	1.000					
Married	0.910	0.801-1.034	0.148			
Race						
White	1.000					
Black	0.862	0.683-1.087	0.210			
Other	0.972	0.792-1.192	0.783			
AJCC						
I	1.000			1.000		
II	1.453	1.11-1.9	0.006	1.698	0.919-3.136	0.999
III	3.434	2.644-4.461	0.000	3.606	1.627-7.993	0.091
IV	7.583	5.776-9.956	0.000	1.475	0.834-2.607	0.002
T						
T1	1.000			1.000		
T2	1.638	1.29-2.08	0.000	1.475	0.834-2.607	0.182
T3	4.619	3.63-5.878	0.000	2.640	1.512-4.609	0.001
T4	6.209	4.008-9.62	0.000	1.956	0.942-4.062	0.072
N						
N0	1.000			1.000		
N1	1.518	1.31-1.759	0.000	0.932	0.779-1.115	0.441
N2	2.611	1.881-3.625	0.000	0.880	0.555-1.395	0.587
M						
M0	1.000			1.000		
M1	3.752	3.218-4.376	0.000	1.257	0.751-2.104	0.384
Radiation						
No/Unknown	1.000					
Yes	0.935	0.782-1.117	0.460			
Chemotherapy						
No/Unknown	1.000					
Yes	1.114	0.971-1.277	0.123			

 10.3389/fonc.2023.1083618

small sample sizes (18–20). Hence, we conducted this population-based study to explore the survival benefit of surgery in GBC patients aged 70 years or older.

The clinicopathological features and survival outcomes of GBC patients in surgery and no-surgery group were compared in this study. We found that patients with better AJCC and TNM stage were more likely to receive surgery (P<0.001). The AJCC and TNM stage are essential factors for judging the degree of tumor progression, choosing treatment decisions, and determining prognosis (21). GBC patients in advanced stages experienced the lowest rates of survival. Previous research demonstrated that patients with distant metastasis had higher mortality risk (HR= 2.392, 95% CI=2.027-2.823, P<.001) (14). Similarly, the present study showed that patients presented with M1 stage experienced higher mortality risk (for OS, M1 vs M0: HR=1.774; for CSS, M1 vs M0: HR=1.862, P<0.001). Subgroup analysis according to AJCC demonstrated that surgery could improve OS and CSS in elderly patients with AJCC III and IV. However, surgery did not affect OS and CSS in AJCC I andIIpatients. This might because of the relative small size of GBC patients with AJCC I andIIincluded in our study. Subgroup analysis also indicated that GBC patients aged 70 years or older with T1-3, any N and M stage could get OS and CSS benefits from surgery. Thus, the AJCC and TNM stage are helpful in selecting patients suitable for surgery and evaluating the prognosis for GBC patients. In addition, our study found that age, AJCC stage, and T stage were prognostic predictors for elderly patients with gallbladder cancer who underwent surgery, which is consistent with previous studies (16, 17, 22). This suggests that a detailed assessment of these factors is an important part of the comprehensive evaluation before receiving surgical treatment. Notably, our study also found that marriage was an independent predictor of OS in patients undergoing surgery and it was not statistically significant for CSS. Patients who are fighting cancer may benefit from the good experience and emotional support that come from marriage. These non-disease-induced interferences were corrected for in the CSS analysis.

In our study, we demonstrated that the cumulative mortality of GBC patients in surgery group was lower than that of no-surgery group, as well as after PSM. Multivariate Cox regression analysis indicated that surgery was a positive predictive factor of OS and CSS in GBC patients (for OS, HR=0.633, 95% CI=0.527-0.761, P<0.001; for CSS, HR=0.607, 95% CI=0.498-0.739, P<0.001). Subgroup analysis according to age was made in our study. Surgery significantly improved OS and CSS in patients aged 70-84 years old (P<0.05), but did not enhance survival in patients aged 85 or older (P>0.05). We assumed that increased age may account for more post-surgery complications, and the usual poorer nutritional status could decrease their resistance to complications. Considering their short remaining survival time, there will be few benefits to perform surgery in GBC patients aged ≥85 years, both patients and physicians had better not take the surgical risks. At the same time, if surgery must be performed inevitably, risk management is essential. Li P et al. showed that patients who underwent gallbladder adenocarcinoma resection older than 65 years may have a relatively poor OS (17). Xu X et al. demonstrated that GBC patients older than 70 years after surgery were also inversely correlated with survival (11). Our study provides further evidence that elderly patients aged 70-84 years with GBC can still benefit significantly from surgical treatment after a reasonable comprehensive evaluation. To our best knowledge, the present study was the first population-based study that systematically clarify the effect of surgery on patients over 70 years of age.

Our research has some strengths. First, our research was based on the SEER database, which collected clinical data from 28% of the US population. This means that our result is supported by a large amount of data. Second, compared with previous studies, our research targeted patients with GBC older than 70 years old. The present study also has some limitations. First, this was a retrospective study based on the SEER database, so selective bias was inevitable. Although we adjusted for confounding bias based on Cox regression, PSM, and subgroup analysis, these methods still failed to correct for potential unknown bias. Second, the SEER database lacks many data on factors such as basic diseases, preoperative physical status, and complications that may have a significant impact on the choice of treatment methods and prognosis of patients. More high-quality prospective studies are needed in the future to validate our conclusions.

5 Conclusion

In conclusion, this study demonstrated that surgery was an independent prognostic factor of OS and CSS for elderly GBC patients (≥70 years old). For patients of 70-84 years old, surgery was associated with improved OS and CSS. Future studies of prospective, randomized and multicenter trials are needed to validate our finding.

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 data of this study is obtained from the SEER database. The patients' data is public and anonymous, so this study does not require ethical approval and informed consent.

Author contributions

XX and QD designed the study. XX collected and analyzed the data. XX drafted the initial manuscript. QD and JW reviewed and edited the article. All authors contributed to the article and approved the submitted version.

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

References

1. Miranda-Filho A, Pineros M, Ferreccio C, Adsay V, Soerjomataram I, Bray F, et al. Gallbladder and extrahepatic bile duct cancers in the americas: Incidence and mortality patterns and trends. *Int J Cancer* (2020) 147(4):978–89. doi: 10.1002/ijc.32863

2. Halaseh SA, Halaseh S, Shakman R. A review of the etiology and epidemiology of gallbladder cancer: What you need to know. *Cureus* (2022) 14(8):e28260. doi: 10.7759/cureus.28260

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

4. Coburn NG, Cleary SP, Tan JC, Law CH. Surgery for gallbladder cancer: A population-based analysis. *J Am Coll Surg* (2008) 207(3):371–82. doi: 10.1016/j.jamcollsurg.2008.02.031

5. Zhang M, Wu C, Zuo B, Gong W, Zhang Y, Yang Y, et al. Trends of gallbladder cancer incidence, mortality, and diagnostic approach in urban shanghai between 1973 and 2009. *Tumori* (2020) 106(5):392–9. doi: 10.1177/0300891619890232

6. Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: Surgical treatment. *J Hepatobiliary Pancreat Surg* (2008) 15(1):41–54. doi: 10.1007/s00534-007-1279-5

7. Al-Refaie WB, Parsons HM, Habermann EB, Kwaan M, Spencer MP, Henderson WG, et al. Operative outcomes beyond 30-day mortality: Colorectal cancer surgery in oldest old. *Ann Surg* (2011) 253(5):947–52. doi: 10.1097/SLA.0b013e318216f56e

8. di Sebastiano P, Festa L, Buchler MW, di Mola FF. Surgical aspects in management of hepato-Pancreatico-Biliary tumours in the elderly. *Best Pract Res Clin Gastroenterol* (2009) 23(6):919–23. doi: 10.1016/j.bpg.2009.10.003

9. Petrowsky H, Clavien PA. Should we deny surgery for malignant hepato-Pancreatico-Biliary tumors to elderly patients? *World J Surg* (2005) 29(9):1093–100. doi: 10.1007/s00268-005-1130-6

10. Papis D, Vagliasindi A, Maida P. Hepatobiliary and pancreatic surgery in the elderly: Current status. *Ann Hepatobiliary Pancreat Surg* (2020) 24(1):1–5. doi: 10.14701/ahbps.2020.24.1.1

11. Xu X, He M, Wang H, Zhan M, Yang L. Development and validation of a prognostic nomogram for gallbladder cancer patients after surgery. *BMC Gastroenterol* (2022) 22(1):200. doi: 10.1186/s12876-022-02281-2

12. Lin Y, Chen H, Pan F. Prognostic nomograms to predict survival of patients with resectable gallbladder cancer: A surveillance, epidemiology, and end results (Seer)-based analysis. *Med Sci Monit* (2021) 27:e929106. doi: 10.12659/MSM.929106

13. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: Comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* (2000) 232(4):557–69. doi: 10.1097/00000658-200010000-00011

14. Zhu X, Zhang X, Hu X, Ren H, Wu S, Wu J, et al. Survival analysis of patients with primary gallbladder cancer from 2010 to 2015: A retrospective study based on seer data. *Med (Baltimore)* (2020) 99(40):e22292. doi: 10.1097/MD.0000000000022292

15. Wang SJ, Lemieux A, Kalpathy-Cramer J, Ord CB, Walker GV, Fuller CD, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* (2011) 29(35):4627–32. doi: 10.1200/JCO.2010.33.8020

16. Xiao Z, Shi Z, Hu L, Gao Y, Zhao J, Liu Y, et al. A new nomogram from the seer database for predicting the prognosis of gallbladder cancer patients after surgery. *Ann Transl Med* (2019) 7(23):738. doi: 10.21037/atm.2019.11.112

17. Li P, Song L. Prognostic evaluation for patients over 45 years old with gallbladder adenocarcinoma resection: A seer-based nomogram analysis. *BioMed Res Int* (2020) 2020:6370946. doi: 10.1155/2020/6370946

18. Yao GL. Laparoscopic hepatopancreaticoduodenectomy for synchronous gallbladder cancer and extrahepatic cholangiocarcinoma: A case report. *World J Surg Oncol* (2022) 20(1):190. doi: 10.1186/s12957-022-02628-9

19. Okumura T, Nakamura J, Kai K, Ide Y, Nakamura H, Koga H, et al. Curative resection of gallbladder cancer with liver invasion and hepatic metastasis after chemotherapy with gemcitabine plus s-1: Report of a case. *World J Surg Oncol* (2014) 12:326. doi: 10.1186/1477-7819-12-326

20. Kim S, Yoon YS, Han HS, Cho JY, Choi Y. Laparoscopic extended cholecystectomy for T3 gallbladder cancer. *Surg Endosc* (2018) 32(6):2984–5. doi: 10.1007/s00464-017-5952-8

21. Cai ZQ, Guo P, Si SB, Geng ZM, Chen C, Cong LL. Analysis of prognostic factors for survival after surgery for gallbladder cancer based on a Bayesian network. *Sci Rep* (2017) 7(1):293. doi: 10.1038/s41598-017-00491-3

22. He C, Cai Z, Zhang Y, Lin X. Prognostic model to predict cancer-specific survival for patients with gallbladder carcinoma after surgery: A population-based analysis. *Front Oncol* (2019) 9:1329. doi: 10.3389/fonc.2019.01329

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 05 May 2023
DOI 10.3389/fsurg.2023.1074980

OPEN ACCESS

EDITED BY
Cosimo Sperti,
University of Padua, Italy

REVIEWED BY
Vikash Raj,
Deoghar (AIIMS Deoghar), India
Jana Fox,
Montefiore Medical Center, United States

*CORRESPONDENCE
Xiaosong Chen
✉ chenxiaosong0156@hotmail.com
Kunwei Shen
✉ kwshen@medmail.com.cn

[†]These authors have contributed equally to this work

RECEIVED 20 October 2022
ACCEPTED 18 April 2023
PUBLISHED 05 May 2023

CITATION
Zhang X, Zeng Y, Wang Z, Chen X and Shen K (2023) Associations of clinicopathological factors with local treatment and survival outcome in elderly patients with ductal carcinoma *in situ*.
Front. Surg. 10:1074980.
doi: 10.3389/fsurg.2023.1074980

Associations of clinicopathological factors with local treatment and survival outcome in elderly patients with ductal carcinoma *in situ*

Xu Zhang[†], Yufei Zeng[†], Zheng Wang, Xiaosong Chen* and Kunwei Shen*

Department of General Surgery, Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: Local treatment for ductal carcinoma *in situ* (DCIS) remains controversial for elderly patients. This study aims to evaluate the association of local treatment, clinicopathological factors, and survival in elderly DCIS patients.
Methods: Patients ≥ 60 years diagnosed with DCIS from January 2009 to December 2018 were retrospectively included. Local treatment including breast surgery, axillary lymph node (ALN) surgery, and radiotherapy were analyzed among subgroups (age of 60–69, 70–79, and ≥ 80 years), and their associations with clinicopathological features and prognostic outcome were further evaluated.
Results: A total of 331 patients were included. Eventually 86 patients received breast conserving surgery (BCS) and 245 patients received mastectomy. ALN surgery was omitted in 62 patients. Age and tumor size were independent factors that influenced the breast and ALN surgery ($P < 0.05$). Compared with patients aging 60–69, patients ≥ 80 years were more likely to receive BCS (OR 4.28, 95% CI 1.33–13.78, $P = 0.015$) and be exempt from ALN surgery (OR 0.19, 95% CI 0.05–0.69, $P = 0.011$). Patients with tumor >1.5 cm were significantly less likely to receive BCS (OR 0.45, 95%CI 0.25–0.83, $P = 0.011$) and more likely to receive ALN surgery (OR 4.41, 95%CI 1.96–10.48, $P = 0.001$) compared to patients with tumor ≤ 1.5 cm. Postoperative radiotherapy was performed in 48.8% patients who received BCS. Age was the only factor that associated with the radiotherapy decision after BCS in elderly DCIS patients ($P = 0.025$). No significant recurrence-free survival difference was observed among patients receiving different local treatments.
Conclusions: Age was related to the choice of local treatment in elderly DCIS patients, but different treatment patterns didn't impact disease outcome.

KEYWORDS

breast cancer, ductal carcinoma *in situ*, elderly, surgery, radiotherapy

Abbreviations
ALN, axillary lymph node; ALND, axillary lymph node dissection; ASCO, American Society of Clinical Oncology; BCS, breast conserving surgery; CAP, College of American Pathologists; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; HER2, human epidermal growth receptor 2; IBTR, loco-regional recurrence; IDC, invasive ductal carcinoma; IHC, immunohistochemistry; LRR, loco-regional recurrence; PR, progesterone receptor; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy.

Introduction

With the widespread application of screening mammography, more ductal carcinoma *in situ* (DCIS) has been detected over the past few decades. Currently, among all the newly-diagnosed breast cancer, one fifth was presented as DCIS (1, 2). Although DCIS was considered a rather indolent lesion itself, approximately 25% to 50% of them will progress into invasive ductal carcinoma (IDC) eventually. So far, the treatment backbone for DCIS is still surgery, in a similar manner as IDC tumor.

Elderly patients usually were presented with more comorbidities, and have relatively shorter life expectancies (3). Normally, a trend of treatment de-escalation exists among elderly breast cancer patients. Elderly patients with DCIS experience lower local recurrence rate than younger patients (4–6), therefore debate remains about how to select the optimal treatment for them. Some suggests that active surveillance may be safe for elderly patients with rather low risk DCIS, in order to avoid overtreatment and reduce morbidity caused by surgery. However, others argue that elderly patients had longer life expectancies now and should be treated with same standard as younger patients (7). Notably, elderly patients themselves are heterogeneous, with or without co-existing illness, and different kinds of illness all render them into different physical condition, resulting in different tolerance of local treatment. Currently, little is known regarding the clinical and pathological factors that contribute to treatment decisions in elderly DCIS patients.

Based on above issue, this study aims to evaluate the current local treatment patterns of elderly patients with DCIS. Also, we aim to explore the factors that influence the choice of local treatment and their associations with prognosis for elderly DCIS patients.

Methods

Study design and patients

Patients treated at the Comprehensive Breast Health Center, Ruijin Hospital from January 2009 and December 2018 were retrospectively reviewed. Elderly patients, defined as those aged ≥ 60 years, with a diagnosis of pure DCIS who received surgery with or without postoperative radiotherapy and had a minimum follow-up time of two years were included in this study. Main exclusion criteria included histologically proven invasive disease, metastatic breast cancer, and previously received treatment for DCIS. Demographic, diagnostic, clinicopathological, local treatment, follow-up and comorbidity information were retrieved from Shanghai Jiao Tong University Breast Cancer Database (SJTU-BCDB). Current study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Ruijin Hospital.

Clinicopathological and follow-up data

All patients included received preoperative x-ray mammography and breast ultrasound evaluation. Full-field digital mammography with cranio-caudal and medio-lateral oblique views was applied and reviewed by experienced radiologists. Patients also underwent ultrasound examination of bilateral breast and axillary lymph nodes. A proportion of patients received breast MRI evaluation in a prone position on scanners having a field strength ≥1.5 T with a specified breast coil. Initial clinical manifestation at diagnosis were characterized as mass symptoms including palpable mass on physical examination or measurable mass on screening ultrasound, and non-mass symptoms including nipple discharge, or radiographic anomaly such as calcification or distortion on mammography. Patients enrolled received either mastectomy or breast conserving surgery (BCS) with definitive negative margin (>2 mm). Axillary lymph node (ALN) surgery, including sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) was allowed. Expression of estrogen receptor (ER) and progesterone receptor (PR)were routinely detected by immunohistochemistry (IHC) in surgical specimens. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guideline recommendations were used as criteria for categorizing ER and PR status (8). Nuclear grade was characterized into well differentiated (Grade I), intermediate (Grade II) or poorly differentiated lesions (Grade III). A recommendation of postoperative treatment including radiotherapy, endocrine therapy, or follow-up for each patient were made by a multidisciplinary consultation. Patients received BCS were considered postoperative radiotherapy. Patients with positive ER status who received BCS were routinely recommend endocrine therapy. For further subgroup analysis, patients were divided into different groups according to age: 60–69, 70–79, and ≥80 years.

Prognostic endpoints in this study included recurrence-free survival (RFS), defined as time from primary surgery to recurrence or metastasis of breast cancer, or death from any cause; and loco-regional recurrence (LRR), defined as time from surgery to ipsilateral local or regional recurrence of either DCIS or invasive breast cancer. Last follow-up was completed by July 2021.

Statistical analysis

All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL). Statistical analyses included Chi-square test and multivariate logistic regression with odds ratio (OR) were used to assess the treatment recommendations in different patient groups. Time to recurrence was demonstrated by Kaplan–Meier curve and compared between groups using log-rank test. Subgroup analyses were performed by age (60–69, 70–79, ≥80 years old), breast surgery type (BCS or mastectomy), ALN surgery (yes or no), and radiotherapy (yes or no) following BCS. All statistical tests were two-tailed and statistical significance was defined as $P < 0.05$.

Results

Patient and clinicopathological characteristics

A total of 331 patients with complete clinicopathological and follow-up data were included in this study, with 242 (73.1%), 67 (20.3%), and 22 (6.6%) patients aged 60–69, 70–79, and ≥80 years, respectively. The mean age was 67.3 years (range, 60–90 years).

Patient and clinicopathological characteristics of the entire population were summarized in Table 1. A total of 60.4% patients presented with mass at diagnosis. According to pathology evaluation, 217 patients (65.6%) had tumors ≤ 1.5 cm, and 222 patients (67.1%) had ER-positive disease. In terms of biopsy method, 190 patients (57.4%) received core needle biopsy for diagnosis prior to surgery, and 141 (42.6%) patients received excisional biopsy prior or during surgery. Regarding comorbidity, 208 of 331 patients (62.8%) were accompanied with at least one co-existing disease (Supplementary Table S1).

Comparison of clinicopathological features among different age subgroups can also be found in Table 1. There was no significant difference in tumor size, manifestation at diagnosis, biopsy method, nuclear grade, ER status, and PR status among three age subgroups (all $P > 0.05$). While significantly more comorbidities ($P < 0.001$) and higher Charlson Comorbidity Index (CCI, $P < 0.001$) were observed in patients aged ≥80 years.

Comparison of local treatment patterns among age groups

Local treatment patterns in elderly DCIS patients were listed in Figure 1. More patients received mastectomy (74.0%) rather than BCS (26.0%) as breast surgery. ALN surgery was performed in 269 (81.3%) patients, including 219 (66.2%) patients receiving SLNB and 50 (15.1%) receiving ALND. Among the 86 patients receiving BCS, only 42 (48.8%) patients were treated with postoperative radiation.

Local treatment patterns were compared among three age subgroups (Figure 2). Patients ≥ 80 received significantly more BCS as breast surgery compared with those aged 60–69 (59.1% vs. 23.1%, $P < 0.001$) and 70–79 years (59.1% vs. 25.4%,

TABLE 1 Patient and clinicopathological characteristics according to age subgroups.

Characteristics	Total, No. (%)	Age			*P*
		60–69, No. (%)	70–79, No. (%)	≥80, No. (%)	
Tumor size (cm)					0.358
≤1.5	217 (65.6%)	158 (65.3%)	41 (61.2%)	18 (81.8%)	
>1.5	114 (34.4)	84 (34.7%)	26 (38.8)	4 (18.2)	
Manifestation at diagnosis					0.246
Mass	200 (60.4%)	143 (59.1%)	40 (59.7%)	17 (77.3%)	
Non-mass	131 (39.6%)	99 (40.9%)	27 (40.3%)	5 (22.7%)	
Biopsy method					0.780
Core needle biopsy	190 (57.4%)	141 (58.3%)	36 (53.7%)	13 (59.1%)	
Excisional biopsy	141 (42.6%)	101 (41.7%)	31 (46.3%)	9 (40.9%)	
Nuclear grade					0.069
Low	78 (23.6%)	54 (22.3%)	18 (26.9%)	6 (27.3%)	
Intermediate	139 (42.0%)	93 (38.4%)	32 (47.7%)	14 (63.6%)	
High	108 (32.6%)	90 (37.2%)	16 (23.9%)	2 (9.1%)	
Unknown	6 (1.8%)	5 (2.1%)	1 (1.5%)	0 (0.0%)	
ER status					0.222
Positive	222 (67.1%)	155 (64.0%)	48 (71.6%)	19 (86.4%)	
Negative	101 (30.5%)	81 (33.5%)	17 (25.4%)	3 (13.6%)	
Unknown	8 (2.4%)	6 (2.5%)	2 (3.0%)	0 (0.0%)	
PR status					0.077
Positive	188 (56.8%)	128 (52.9%)	42 (62.7%)	18 (81.8%)	
Negative	135 (40.8%)	108 (44.6%)	23 (34.3%)	4 (18.2%)	
Unknown	8 (2.4%)	6 (2.5%)	2 (3.0%)	0 (0.0%)	
Number of comorbidities					**<0.001**
0	123 (37.2%)	105 (43.3%)	13 (19.4%)	5 (22.7%)	
1	112 (33.8%)	80 (33.1%)	26 (38.8%)	6 (27.3%)	
≥2	96 (29.0%)	57 (23.6%)	28 (41.8%)	11 (50.0%)	
CCI					**<0.001**
2	195 (58.9%)	195 (80.6%)	0 (0.0%)	0 (0.0%)	
3	93 (28.1%)	40 (16.5%)	38 (56.7%)	15 (68.2%)	
≥4	43 (13.0%)	7 (2.9%)	29 (43.3%)	7 (31.8%)	

ER, estrogen receptor; PR, progesterone receptor; CCI, Charlson Comorbidity Index.
Values of statistically significance, defined as *P*<0.05, were shown in bold.

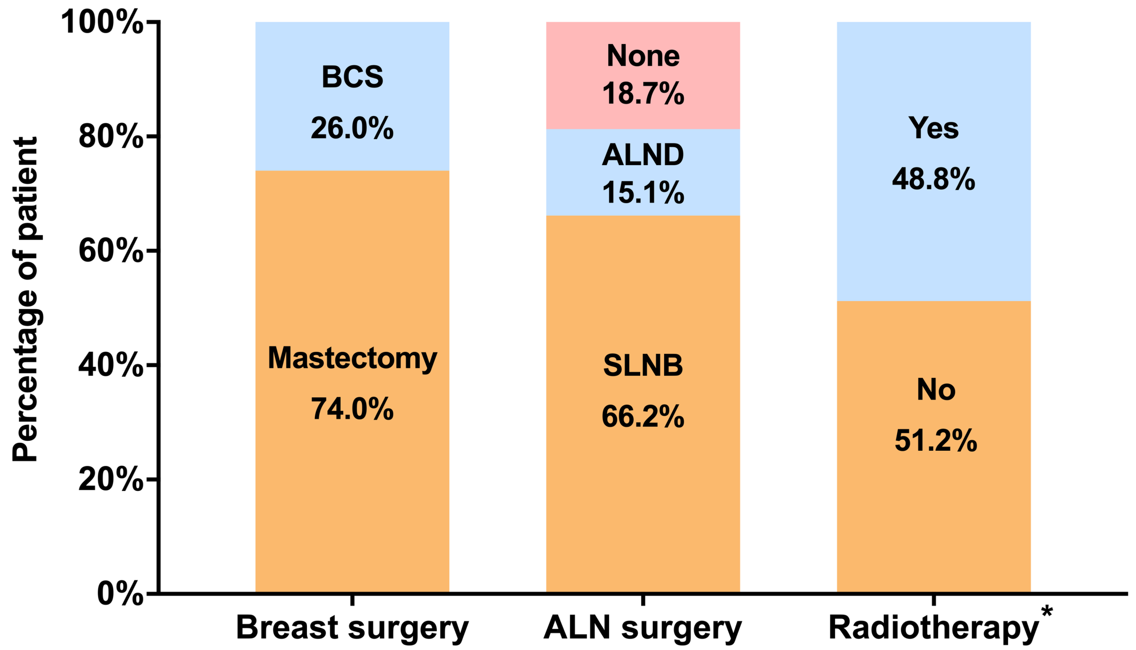


FIGURE 1
Distribution of local treatment patterns in elderly patients with DCIS. *Radiotherapy was considered in patients receiving BCS. (BCS, breast-conserving surgery; ALN, axillary lymph node; SLNB, sentinel lymph node biopsy, ALND, axillary lymph node dissection).

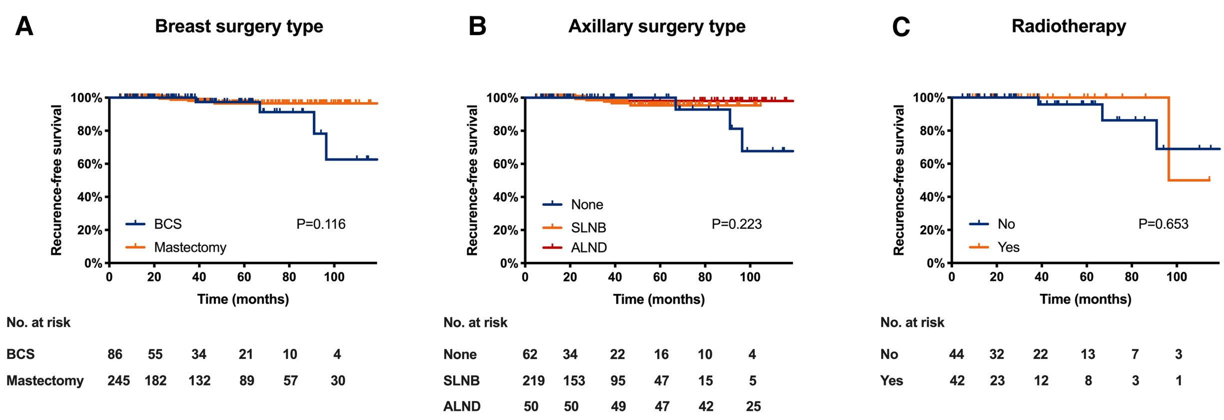


FIGURE 2
Distribution of local treatment methods by age subgroup. (A) distribution of breast surgery type; (B) distribution of axillary lymph node surgery; (C) distribution of radiotherapy in patients received BCS. (BCS, breast conserving surgery, SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection).

$P = 0.006$). They also received less ALN surgery compared with patients aged 60–69 (50.0% vs. 16.1%, $P < 0.001$) and 70–79 years (50.0% vs. 17.9%, $P = 0.010$). For patients receiving BCS, omitting postoperative radiotherapy were more common in patients ≥ 80 compared with those aged 60–69 (84.6% vs. 42.9%, $P = 0.007$).

Factors influencing breast surgery type

Age, tumor size, and manifestation at diagnosis were all significantly associated with the choice of breast surgery type according to univariate analysis (Supplementary Table S2). The proportion of patients receiving BCS were significantly different among 60–69, 70–79, and ≥ 80 age subgroups ($P = 0.001$). Patients with tumor size ≤ 1.5 cm received more BCS than those with tumor size >1.5 cm (30.4% vs. 17.5%, $P = 0.011$). In addition, the percentage of BCS was higher in patients presenting with mass at diagnosis than those with non-mass lesion (30.0% vs. 19.8%, $P = 0.039$).

Multivariate analysis demonstrated that age, tumor size, and manifestation at diagnosis remained to be independent factors for breast surgery type choice (Table 2). Compared with patients aged 60–69, those aged ≥ 80 were more likely to receive BCS [odds ratio (OR) 4.28, 95%CI 1.33–13.78; $P = 0.015$]. Patients with tumor > 1.5 cm were less likely to receive BCS compared with patients who had tumor ≤ 1.5 cm (OR 0.45, 95%CI 0.25–0.83; $P = 0.011$). Furthermore, BCS was more commonly performed in patients presenting with mass at diagnosis than those presenting with non-mass lesion (OR 1.96, 95%CI 1.11–3.45; $P = 0.021$). However, comorbidity and CCI had no significant effect on breast surgery choice for elderly patients with DCIS (both $P > 0.05$).

Factors influencing the choice of ALN surgery

Regarding axillary evaluation, age, tumor size, and breast biopsy type were all significantly related with the choice of ALN surgery in univariate analysis (Supplementary Table S2). Patients ≥ 80 were less likely to receive ALN surgery than those aged 60–69 and 70–79 (50% vs. 83.9% and 82.1%, $P < 0.001$). Patients with tumor >1.5 cm received more ALN surgery than patients with tumor ≤ 1.5 cm (93.9% vs. 74.7%, $P < 0.001$). In addition, ALN surgery was differently omitted in patients who received core needle biopsy and those directly received excisional biopsy (12.6% vs. 27.0%, $P = 0.001$).

Multivariate analysis revealed that age, tumor size, and breast biopsy type all remained to be independent predictors for performing ALN surgery (all $P < 0.05$, Table 2). Patients ≥ 80 were more often exempt from ALN surgery compared to those aged 60–69 (OR 0.19, 95%CI 0.05–0.69; $P = 0.011$). Patients with tumor >1.5 cm were more likely to receive ALN surgery than patients with tumor ≤ 1.5 cm (OR 4.41, 95%CI 1.96–10.48; $P = 0.001$). As for breast biopsy type, excisional biopsy led to a higher probability to omit ALN surgery compared with core needle biopsy (OR 0.47, 95%CI 0.25–0.87; $P = 0.017$).

Factors influencing the decision of radiotherapy following BCS

Postoperative radiotherapy in elderly DCIS patients received BCS were commonly modified. Age was the only factor that significantly associated with the choice of radiotherapy following BCS ($P = 0.025$, Table 3). Compared with 60–69 age subgroup, patients ≥80 years were less likely to receive postoperative radiation (OR 0.14, 95%CI 0.27–0.67; $P = 0.014$). However, comorbidity and CCI were not associated with the decision of radiotherapy in elderly DCIS patients who received BCS (both $P > 0.05$).

Prognostic outcomes according to local treatment

In the study population, 72 of 331 (21.7%) patients underwent BCS had ER-positive disease. All these patients received standard endocrine treatment, among which 27 patients received aromatase inhibitor and 45 received tamoxifen. After a median follow-up of 52.2 months, 2 (0.6%) LRR events, 4 (1.2%) contralateral breast cancer, 1 (0.3%) distant metastasis, and 7 (2.1%) deaths were observed in the cohort (Supplementary Table S3). Among the 7 death events, 1 was breast cancer-related death, and 6 were death from other causes. RFS was statistically different among 60–69, 70–79, and ≥80 subgroups ($P < 0.001$, Supplementary Figure S1A). However, LRR was similar for patients aging 60–69, 70–79, and ≥80 ($P = 0.698$, Supplementary Figure S1B).

Clinical outcomes were similar among patients receiving different local treatments (Figure 3). Comparable RFS was observed between patients receiving mastectomy and BCS ($P = 0.146$, Figure 3A). Similarly, patients receiving no ALN surgery, SLNB or ALND had comparable RFS ($P = 0.363$, Figure 3B). For patients underwent BCS, receiving radiotherapy or not have no significant impact on RFS ($P = 0.468$, Figure 3C).

TABLE 2 Multivariate analysis of characteristics associated with different surgery types.

Variables	Receiving BCS[a]		Receiving ALN surgery[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age		**0.030**		**0.016**
70–79 vs. 60–69 years	1.24 (0.46–3.35)	0.669	0.81 (0.25–2.63)	0.720
≥80 vs. 60–69 years	4.28 (1.33–13.78)	**0.015**	0.19 (0.05–0.69)	**0.011**
Tumor size >1.5 cm vs. ≤ 1.5 cm	0.45 (0.25–0.83)	**0.011**	4.41 (1.96–10.48)	**0.001**
Number of comorbidities		0.110		0.472
1 vs. 0	1.55 (0.82–2.95)	0.180	0.67 (0.32–1.38)	0.278
≥2 vs. 0	2.32 (1.05–5.15)	**0.038**	0.62 (0.25–1.55)	0.304
CCI		0.811		0.648
3 vs. 2	0.75 (0.31–1.80)	0.518	1.40 (0.49–4.01)	0.534
≥4 vs. 2	0.74 (0.19–2.80)	0.654	0.97 (0.20–4.64)	0.965
Mass vs. non-mass at diagnosis	1.96 (1.11–3.45)	**0.021**	0.89 (0.48–1.66)	0.708
Excisional biopsy vs. core needle biopsy	1.11 (0.65–1.91)	0.703	0.47 (0.25–0.87)	**0.017**

ALN, axillary lymph node.
CCI, Charlson comorbidity index.
[a]As compared to receiving mastectomy.
[b]As compared to receiving no ALN surgery.
Values of statistically significance, defined as $P<0.05$, were shown in bold.

TABLE 3 Clinicopathological characteristics associated with adjuvant radiotherapy in patients receiving breast conserving surgery.

Characteristics	Yes ($n = 42$)	No ($n = 44$)	*P*
Age (years)			0.025
60–69	32 (57.1%)	24 (42.9%)	
70–79	8 (47.1%)	9 (52.9%)	
≥80	2 (15.4%)	11 (84.6%)	
Tumor size (cm)			0.254
≤1.5	30 (45.5%)	36 (54.5%)	
>1.5	12 (60.0%)	8 (40.0%)	
Number of comorbidities			0.095
0	15 (62.5%)	9 (37.5%)	
1	16 (53.3%)	14 (46.7%)	
≥2	11 (34.4%)	21 (65.6%)	
CCI			0.139
2	26 (57.8%)	19 (42.2%)	
3	12 (44.4%)	15 (55.6%)	
≥4	4 (28.6%)	10 (71.4%)	
Manifestation at diagnosis			0.743
Mass	30 (50.0%)	30 (50.0%)	
No mass	12 (46.2%)	14 (53.8%)	
Nuclear grade			0.701
Low	12 (44.4%)	15 (55.6%)	
Intermediate	19 (41.3%)	27 (58.7%)	
High	11 (91.7%)	1 (8.3%)	
Unknown	0 (0.0%)	1 (100.0%)	
ER status			0.113
Positive	8 (66.7%)	4 (33.3%)	
Negative	32 (44.4%)	40 (55.6%)	
Unknown	2 (100.0%)	0 (0.0%)	
PR status			0.303
Positive	9 (52.9%)	8 (47.1%)	
Negative	31 (46.3%)	36 (53.7%)	
Unknown	2 (100.0%)	0 (0.0%)	

CCI, Charlson comorbidity index; ER, estrogen receptor; PR, progesterone receptor.
Values of statistically significance, defined as $P<0.05$, were shown in bold.

Discussion

The relatively indolent nature and good prognosis of DCIS raises concerns on its over-diagnosis and overtreatment, especially among elderly patients (9, 10). In this study, we found that age rather than comorbidity status significantly influence the choice of local treatments. Elderly DCIS patients appear to receive less aggressive surgery type and less adjuvant radiotherapy after BCS, but without impaired disease outcome.

Currently it's acknowledged that DCIS is a precursor lesion to most, if not all, invasive breast cancer (11). However, this progression is usually unpredictable and a considerable percentage of DCIS lesions will never become invasive (2). Compared with younger DCIS patients, the recurrence rate of DCIS in older women is lower. Considering limited life expectancy in elderly patients, less aggressive treatments are usually recommended (12, 13). However, the appropriate local treatment for elderly patients with DCIS is still controversial. Debate remains about the feasibility to choose active monitoring in substitution for surgery, to omit radiotherapy after BCS, or to spare axillary evaluation during mastectomy (14). Moreover, evidence is still scarce regarding factors influencing the choice of different local treatment.

Surgery is still regarded as the primary treatment for DCIS tumors. Although DCIS patients are eligible for either mastectomy or breast conserving surgery with equivalent safety and survival benefit (15), more than half of cases in our cohort underwent mastectomy, which is consistent with previous reports (16). Bleicher et al. found that older women with DCIS chose mastectomy over breast-conserving treatment if they have larger tumor size, lower education level, or consulted greater number of surgeons, while age and comorbidities did not predict choosing mastectomy (3). According to our results, patients older than 80 years were more likely to receive BCS than mastectomy. Moreover, patients with tumor size larger than 1.5 cm or primarily presented with mass symptom were less likely to receive BCS. This was not unexpected as for larger tumors, as BCS may be difficult to achieve clear resection margin. Among well-established risk factors for local recurrence in DCIS including histologic subtype, nuclear grade, and age, etc., margin status was described as the most important one (17, 18). Although tumor size was not identified as the predicting factor for LRR in DCIS according to NSABP B-17 or EORTC trials (19, 20), it is anticipated that larger tumor size and non-mass lesion might indicate an extensive lesion requiring mastectomy to ensure clear margin status. In this study, more than half (71%) patients received preoperative breast MRI evaluation, which

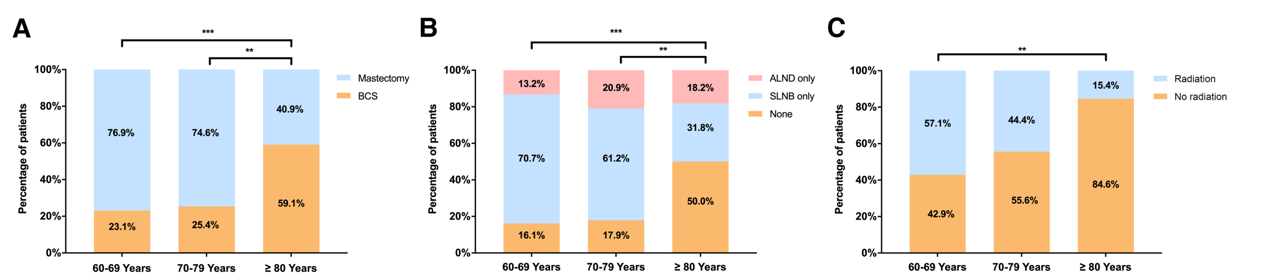


FIGURE 3
Recurrence-free survival in elderly patients with DCIS by (A) breast surgery; (B) ALN surgery; and (C) radiotherapy following BCS. (BCS, breast conserving surgery, SLNB, sentinel lymph node biopsy, ALND, axillary lymph node dissection).

might identify non-mass enhancement beyond target lesion found by mammography or ultrasound. Application of preoperative MRI were probably associated with decreased breast-conserving rate in this study. In addition, co-existing cardiovascular diseases would raise concern when considering radiotherapy after BCS. Patient's preference is an important factor that determine surgery type in China. Surgery type, BCS or mastectomy, was usually discussed by patients and her family members. Elderly patients care less about cosmetics but more about side effects and economics of radiotherapy. Therefore, mastectomy could be an option (21, 22).

As recommended, mastectomy is routinely accompanied by axillary evaluation for DCIS cases because subsequent sentinel lymph node biopsy would be difficult to perform if an invasive disease was found on postoperative pathological specimen (23). Especially in patients diagnosed with core needle biopsy since limited sample may lead to pathological underestimation (24). Consistently, in our study, compared with patients receiving excisional biopsy, patients receiving core needle biopsy prior to surgery were more likely to underwent axillary evaluation. We also observed that the percentage of patients receiving ALN surgery were significantly higher in mastectomy subgroup than BCS subgroup.

Less axillary evaluation was performed in elderly patients according to our results, especially for those older than 80 years. Furthermore, our study demonstrated that receiving ALN surgery or not have no impact on local recurrence. DCIS patients usually have no clinically detected lymph node. Although the final pathological diagnosis might be upgraded to invasive cancer, axillary lymph node metastasis and regional recurrence is still scarce for DCIS patients (19, 25). We admitted that the proportion of patients who received ALN surgery is relatively high. However, the real-world clinical practice in China is somewhat difficult to follow the treatment standard of DCIS, which did not recommend routine axillary evaluation for DCIS patients, especially for those received BCS. Chinese patients usually refuse a secondary ALN surgery if invasive disease is detected pathologically after primary surgery. Therefore, most patients demand ALN evaluation at the same time when they received breast surgery. Some radical patients request for a total mastectomy and axillary lymph node dissection even if no invasive breast cancer was found in preoperative biopsy. Though there exist the worries on a second surgery or locoregional recurrence from patients, the rate of upstaging from DCIS to invasive disease has been reported less than 20%. Most upstaged disease were Stage IA invasive ductal carcinoma, which have low risk of nodal metastasis (26). In recent years, we took great effort in patient education and found that the proportion of ALN surgery decreased in DCIS patients. Therefore, it is reasonable to presume ALN surgery could be omitted when performing BCS for elderly DCIS patients.

The benefit brought by postoperative radiotherapy in DCIS patients must be carefully weighed against the accompanying complications (27). With the development of modern radiation techniques, radiotherapy has been proved to be safe and has minimal impact on quality of life, and leading to limited cardiovascular mortality for the elderly (28–30). However, worries on deterioration of their comorbidities and inconvenient daily hospital visits for radiotherapy still trouble specialists and patients. According to our results, more than half of all patients were omitted of postoperative radiotherapy after BCS, and for patients older than 80 years, up to 84.6% were precluded with adjuvant radiotherapy. Age was the only factor related to radiotherapy after BCS. Consistently, Smith et al. had also observed that the proportion of receiving adjuvant radiotherapy decreased while patient age increased (31). Their study reported an omission of radiotherapy after BCS in 51.0% of all patients and 36.8%, 49.9% and 70.8% in patients aging 66–69, 70–79 and ≥80, respectively ($P < 0.001$).

A number of randomized clinical trials have already demonstrated that adding radiotherapy after surgery for DCIS patients of all ages could improve local control rate, which could reduce IBTR by approximately half (19, 32–36). However, the survival benefit brought by radiotherapy in elderly patients, especially patients over 80 years remained controversial. Smith et al. (31) found that radiotherapy after BCS contributed to a significant reduction in LRR in a group of DCIS patients over 65 years old. According to age subgroups, they found that healthy women of 66–79 years old were twice as likely to benefit from radiotherapy than patients ≥85 years who have moderate to severe comorbidity, leaving the benefit of radiotherapy for patients with rather old age no less debatable (31). Also, an EBCTCG meta-analysis had showed that radiotherapy resulted in a greater reduction in LRR for DCIS patients older than 50 years when compared with younger women, while no further study was conducted among patients with age over 65 or more (36).

On the contrary of supporting adjuvant radiotherapy for elderly patients, a study by Ho et al.(37) reported no LRR difference between patients receiving radiotherapy or not in women older than 60 years. Likewise, our study also found that elderly patients with different local treatment modalities (mastectomy, BCS plus radiotherapy, or BCS alone) shared similar LRR. Moreover, none of the patients ≥80 years in our study experienced LRR during follow-up. According to our inclusion criteria and clinicopathological characteristics, the high percentage of negative margin status and low Ki-67 index of enrolled patients probably reduced the potential benefit from radiotherapy (38). The role of adjuvant radiotherapy for elderly DCIS patients warrants further investigation since available evidence is limited.

DCIS is a group of disease with heterogeneous natural course and prognosis. A lot of effort has been made in risk stratification in order to identify a group of DCIS patients with good prognosis, in whom surgical excision alone or even observation could be enough to achieve a satisfactory local control. According to available prognostic factors for DCIS, older age could predict decreased risk of recurrence. Prognostic scores or multigene assays could also be used to evaluated the local control benefit offered by radiotherapy after BCS in DCIS patients (22, 39–42). In future perspective, local treatment strategies may be tailored according to recurrence stratification model in order to balance benefit and risk.

Our study has several limitations. Firstly, the number of patients included in our study was limited. And our follow-up time is relatively short, given the long natural history of DCIS. Therefore, the small number of outcome events may not provide sufficient statistical power to detect the benefit conferred by treatment. Secondly, this is a single institution retrospective study. Large-scaled prospective studies are warranted to validate our results.

In summary, our study presents the current approach of local treatment in elderly DCIS patients. Age is related with the choice of breast surgery, ALN surgery, and postoperative radiotherapy. DCIS patients with age ≥80 years old receive less aggressive local treatments but have no impaired disease outcome.

Data availability statement

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

Ethics statement

The current study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Ruijin Hospital. Informed consent was obtained from each patient.

Author contributions

XC, KS, XZ, YZ, ZW contributed to the concept and design of the study. XZ, YZ and ZW collected, analysed and interpreted the data of patients. XZ and YZ were responsible for the paper drafting, and ZW, XC and KS revised the paper. All authors read and approved the final paper. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81772797); Shanghai Municipal Education Commission—Gaofeng Clinical Medicine Grant Support (No. 20172007); and Ruijin Hospital, Shanghai Jiao Tong University School of Medicine—“Guangci Excellent Youth Training Program” (No. GCQN-2017-A18). The funders had no role in study design, data collection, data analysis, article writing, or article submission.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1074980/full#supplementary-material.

References

1. Kuerer HM, Albarracin CT, Yang WT, Cardiff RD, Brewster AM, Symmans WF, et al. Ductal carcinoma in situ: state of the science and roadmap to advance the field. *J Clin Oncol.* (2009) 27:279–88. doi: 10.1200/JCO.2008.18.3103

2. Ward EM, DeSantis CE, Lin CC, Kramer JL, Jemal A, Kohler B, et al. Cancer statistics: breast cancer in situ. *CA Cancer J Clin.* (2015) 65:481–95. doi: 10.3322/caac.21321

3. Bleicher RJ, Abrahamse P, Hawley ST, Katz SJ, Morrow M. The influence of age on the breast surgery decision-making process. *Ann Surg Oncol.* (2008) 15:854–62. doi: 10.1245/s10434-007-9708-x

4. Vicini FA, Recht A. Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: a critical review of the literature. *J Clin Oncol.* (2002) 20:2736–44. doi: 10.1200/JCO.2002.07.137

5. Kerlikowske K, Molinaro A, Cha I, Ljung BM, Ernster VL, Stewart K, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. *J Natl Cancer Inst.* (2003) 95:1692–702. doi: 10.1093/jnci/djg097

6. Solin LJ, Fourquet A, Vicini FA, Taylor M, Olivotto IA, Haffty B, et al. Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. *Cancer.* (2005) 103:1137–46. doi: 10.1002/cncr.20886

7. Merrill AL, Esserman L, Morrow M. Clinical decisions. Ductal carcinoma in situ. *N Engl J Med.* (2016) 374:390–2. doi: 10.1056/NEJMclde1512213

8. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and progesterone receptor testing in breast cancer: american society of clinical oncology/college of American pathologists guideline update. *Arch Pathol Lab Med.* (2020) 144:545–63. doi: 10.5858/arpa.2019-0904-SA

9. Esserman LJ, Thompson IM Jr., Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. *JAMA.* (2013) 310:797–8. doi: 10.1001/jama.2013.108415

10. Benson JR, Jatoi I, Toi M. Treatment of low-risk ductal carcinoma in situ: is nothing better than something? *Lancet Oncol.* (2016) 17:e442–e51. doi: 10.1016/S1470-2045(16)30367-9

11. Espina V, Liotta LA. What is the malignant nature of human ductal carcinoma in situ? *Nat Rev Cancer.* (2011) 11:68–75. doi: 10.1038/nrc2950

12. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrida S, et al. Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopasual patients. *Cancer.* (2004) 101:1302–10. doi: 10.1002/cncr.20535

13. Muss HB. Adjuvant chemotherapy in older women with breast cancer: who and what? *J Clin Oncol*. (2014) 32:1996–2000. doi: 10.1200/JCO.2013.54.8586

14. van Seijen M, Lips EH, Thompson AM, Nik-Zainal S, Futreal A, Hwang ES, et al. Ductal carcinoma in situ: to treat or not to treat, that is the question. *Br J Cancer*. (2019) 121:285–92. doi: 10.1038/s41416-019-0478-6

15. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. (2005) 366:2087–106. doi: 10.1016/S0140-6736(05)67887-7

16. Wyld L, Garg DK, Kumar ID, Brown H, Reed MW. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. *Br J Cancer*. (2004) 90:1486–91. doi: 10.1038/sj.bjc.6601742

17. Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European organization for research and treatment of cancer trial 10853. *J Clin Oncol*. (2001) 19:2263–71. doi: 10.1200/JCO.2001.19.8.2263

18. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med*. (1999) 340:1455–61. doi: 10.1056/NEJM199905133401902

19. Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from national surgical adjuvant breast and bowel project B-17. *J Clin Oncol*. (1998) 16:441–52. doi: 10.1200/JCO.1998.16.2.441

20. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC breast cancer cooperative group and EORTC radiotherapy group. *Lancet*. (2000) 355:528–33. doi: 10.1016/S0140-6736(99)06341-2

21. Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the eastern cooperative oncology group. *J Clin Oncol*. (2009) 27:5319–24. doi: 10.1200/JCO.2009.21.8560

22. Solin LJ, Gray R, Baehner FL, Butler SM, Hughes LL, Yoshizawa C, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst*. (2013) 105:701–10. doi: 10.1093/jnci/djt067

23. Tunon-de-Lara C, Chauvet MP, Baranzelli MC, Baron M, Piquenot J, Le-Bouédec G, et al. The role of sentinel lymph node biopsy and factors associated with invasion in extensive DCIS of the breast treated by mastectomy: the cinnamome prospective multicenter study. *Ann Surg Oncol*. (2015) 22:3853–60. doi: 10.1245/s10434-015-4476-5

24. Pilewskie M, Karsten M, Radosa J, Eaton A, King TA. Is sentinel lymph node biopsy indicated at completion mastectomy for ductal carcinoma in situ? *Ann Surg Oncol*. (2016) 23:2229–34. doi: 10.1245/s10434-016-5145-z

25. Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol*. (2012) 30:1268–73. doi: 10.1200/JCO.2010.34.0141

26. Lars JG, Marc DR, Ann HP, Alastair MT, Jeremy ST, Jelle W, et al. Surgical upstaging rates for vacuum assisted biopsy proven DCIS: implications for active surveillance trials. *Ann Surg Oncol*. (2017) 24:3534–40. doi: 10.1245/s10434-017-6018-9

27. Barrio AV, Van Zee KJ. Controversies in the treatment of ductal carcinoma in situ. *Annu Rev Med*. (2017) 68:197–211. doi: 10.1146/annurev-med-050715-104920

28. Rayan G, Dawson LA, Bezjak A, Lau A, Fyles AW, Yi QL, et al. Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy. *Int J Radiat Oncol Biol Phys*. (2003) 55:154–61. doi: 10.1016/S0360-3016(02)03826-9

29. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. (2013) 368:987–98. doi: 10.1056/NEJMoa1209825

30. Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. *Br Med J*. (2003) 326:256–7. doi: 10.1136/bmj.326.7383.256

31. Smith BD, Haffty BG, Buchholz TA, Smith GL, Galusha DH, Bekelman JE, et al. Effectiveness of radiation therapy in older women with ductal carcinoma in situ. *J Natl Cancer Inst*. (2006) 98:1302–10. doi: 10.1093/jnci/djj359

32. Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst*. (2011) 103:478–88. doi: 10.1093/jnci/djr027

33. Donker M, Litiere S, Werutsky G, Julien JP, Fentiman IS, Agresti R, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol*. (2013) 31:4054–9. doi: 10.1200/JCO.2013.49.5077

34. Warnberg F, Garmo H, Emdin S, Hedberg V, Adwall L, Sandelin K, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS trial. *J Clin Oncol*. (2014) 32:3613–8. doi: 10.1200/JCO.2014.56.2595

35. McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol*. (2015) 33:709–15. doi: 10.1200/JCO.2014.57.9029

36. Early Breast Cancer Trialists' Collaborative G, Correa C, McGale P, Taylor C, Wang Y, Clarke M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr*. 2010;2010:162–77. doi: 10.1093/jncimonographs/lgq039

37. Ho A, Goenka A, Ishill N, Van Zee K, McLane A, Gonzales AM, et al. The effect of age in the outcome and treatment of older women with ductal carcinoma in situ. *Breast*. (2011) 20:71–7. doi: 10.1016/j.breast.2010.07.005

38. Lazzeroni M, Guerrieri-Gonzaga A, Botteri E, Leonardi MC, Rotmensz N, Serrano D, et al. Tailoring treatment for ductal intraepithelial neoplasia of the breast according to Ki-67 and molecular phenotype. *Br J Cancer*. (2013) 108:1593–601. doi: 10.1038/bjc.2013.147

39. Silverstein MJ, Lagios MD. Choosing treatment for patients with ductal carcinoma in situ: fine tuning the university of southern California/van nuys prognostic Index. *J Natl Cancer Inst Monogr*. (2010) 2010:193–6. doi: 10.1093/jncimonographs/lgq040

40. Rudloff U, Jacks LM, Goldberg JI, Wynveen CA, Brogi E, Patil S, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. *J Clin Oncol*. (2010) 28:3762–9. doi: 10.1200/JCO.2009.26.8847

41. Sagara Y, Freedman RA, Vaz-Luis I, Mallory MA, Wong SM, Aydogan F, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. *J Clin Oncol*. (2016) 34:1190–6. doi: 10.1200/JCO.2015.65.1869

42. Rakovitch E, Nofech-Mozes S, Hanna W, Baehner FL, Saskin R, Butler SM, et al. A population-based validation study of the DCIS score predicting recurrence risk in individuals treated by breast-conserving surgery alone. *Breast Cancer Res Treat*. (2015) 152:389–98. doi: 10.1007/s10549-015-3464-6

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 12 May 2023
DOI 10.3389/fonc.2023.1104109

Check for updates

OPEN ACCESS

EDITED BY
Jinqiu Jacky Yuan,
Sun Yat-sen University, China

REVIEWED BY
Letizia Laface,
Ospedale di Carate Brianza, ASST Vimercate, Italy
Ming Zheng,
Academy of Military Medical Sciences, China
Masaichi Ohira,
Osaka City University, Japan

*CORRESPONDENCE
Lucia Moletta
lucia.moletta@unipd.it

†These authors share first authorship

‡These authors share last authorship

RECEIVED 21 November 2022
ACCEPTED 21 April 2023
PUBLISHED 12 May 2023

CITATION
Capovilla G, Uzun E, Scarton A, Moletta L, Hadzijusufovic E, Provenzano L, Salvador R, Pierobon ES, Zanchettin G, Tagkalos E, Berlth F, Lang H, Valmasoni M and Grimminger PP (2023) Minimally invasive Ivor Lewis esophagectomy in the elderly patient: a multicenter retrospective matched-cohort study.
Front. Oncol. 13:1104109.
doi: 10.3389/fonc.2023.1104109

Minimally invasive Ivor Lewis esophagectomy in the elderly patient: a multicenter retrospective matched-cohort study

Giovanni Capovilla[1†], Eren Uzun[2†], Alessia Scarton[1], Lucia Moletta[1*], Edin Hadzijusufovic[2], Luca Provenzano[1], Renato Salvador[1], Elisa Sefora Pierobon[1], Gianpietro Zanchettin[1], Evangelos Tagkalos[2], Felix Berlth[2], Hauke Lang[2], Michele Valmasoni[1‡] and Peter P. Grimminger[2‡]

[1]Department of Surgery, Oncology and Gastroenterology (DiSCOG), Padova University Hospital, Padova, Italy, [2]Department of General, Visceral and Transplant Surgery, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Introduction: Several studies reported the advantages of minimally invasive esophagectomy over the conventional open approach, particularly in terms of postoperative morbidity and mortality. The literature regarding the elderly population is however scarce and it is still not clear whether elderly patients may benefit from a minimally invasive approach as the general population. We sought to evaluate whether thoracoscopic/ laparoscopic (MIE) or fully robotic (RAMIE) Ivor-Lewis esophagectomy significantly reduces postoperative morbidity in the elderly population.

Methods: We analyzed data of patients who underwent open esophagectomy or MIE/RAMIE at Mainz University Hospital and at Padova University Hospital between 2016 and 2021. Elderly patients were defined as those ≥ 75 years old. Clinical characteristics and the postoperative outcomes were compared between elderly patients who underwent open esophagectomy or MIE/RAMIE. A 1-to-1 matched comparison was also performed. Patients < 75 years old were evaluated as a control group.

Results: Among elderly patients MIE/RAMIE were associated with a lower overall morbidity (39.7% vs. 62.7%, p=0.005), less pulmonary complications (32.8 vs. 56.9%, p=0.003) and a shorter hospital stay (13 vs. 18 days, p=0.03). Comparable findings were obtained after matching. Similarly, among < 75 years-old patients, a reduced morbidity (31.2% vs. 43.5%, p=0.01) and less pulmonary complications (22% vs. 36%, p=0.001) were detected in the minimally invasive group.

Discussion: Minimally invasive esophagectomy improves the postoperative course of elderly patients reducing the overall incidence of postoperative complications, particularly of pulmonary complications.

KEYWORDS

MIE, RAMIE, laparoscopy, thoracoscopy, esophagectomy, esophageal cancer

1 Introduction

Ivor Lewis esophagectomy is a complex procedure, burdened by a high rate of postoperative complications and mortality (1–3). The use of a minimally invasive approach has been associated with better perioperative outcomes, however most of the published studies are conducted on the general population (4–6) and the literature evaluating the outcomes in elderly patients is rather limited (7–10). Furthermore, most of the available data focus on the differences in the postoperative outcomes between groups of elderly and non-elderly patients (7–9), while the evaluation of the benefits provided by a minimally invasive approach compared to open surgery within the different age groups is seldom performed (10). Elderly subjects represent indeed a fragile subset, often presenting in worse clinical conditions and with a poor performance status. It is therefore not clear whether the same improvement in the postoperative course seen in the general population undergoing minimally invasive esophagectomy could be expected in older individuals.

Aim of our study was to evaluate the short-term postoperative outcome of minimally invasive Ivor Lewis esophagectomy and to assess whether the use of this approach provides the same improvement in the postoperative course for both elderly and non-elderly patients.

2 Methods

2.1 Study population

We retrospectively reviewed prospectively collected records from 2016 to 2021 of all patients with esophageal cancer who referred to two high volume centers for upper-GI surgery: Mainz University Hospital (Germany) and Padova University Hospital (Italy) and underwent Ivor-Lewis esophagectomy with either an open or a laparoscopic/thoracoscopic approach (minimally invasive esophagectomy, MIE) or a fully robotic approach (robotic-assisted minimally invasive esophagectomy, RAMIE).

Only patients with esophageal squamous cell carcinoma (ESCC) or adenocarcinoma (EAC) were considered recruitable. Patients with cT4b or M+ disease, patients with cervical or Siewert 3 cancers and those who underwent R2, or palliative resections were excluded from the study. Patients who underwent upfront surgery or multimodal treatment comprising chemotherapy (CT) and/or radiotherapy (RT) and surgery were recruited.

2.2 Study design

Elderly patients were defined as those who were ≥ 75 years old at the time of surgery (≥ 75y group) and represented the study group. The control group consisted of patients being < 75 years old at surgery (< 75y group). Differences in the clinical characteristics of the two groups were compared by univariate analysis. A subset analysis of the ≥ 75y group was performed comparing the clinical characteristics and the postoperative outcome of elderly patients who underwent open esophagectomy (≥ 75y open group) and MIE/RAMIE (≥ 75y MI group). The same analysis was performed within the control group (< 75y open group vs. < 75y MI group).

The univariate analysis of preoperative and postoperative outcomes was then repeated within the ≥ 75y group after one-to-one matching between the ≥ 75y open group and the ≥ 75y MI group. The two subgroups were matched for the following potential confounding factors: age, sex, ASA score, cancer histology, cancer location and preoperative treatment. Primary outcome of the study were the short-term post-surgical morbidity and mortality.

2.3 Collected data and definitions

EAC and ESCC were graded according to AJCC 8th edition Classification (11). The overall patients' preoperative condition was assessed using the Karnofsky performance status (KPS) (12); the operative risk was evaluated using the American Society of Anestesiology (ASA) classification (13) and the Charlson's Comorbidity Index (CCI) (14).

Post-operative 90-day complications were assessed according to the Esophagectomy Complications Consensus Group ECCG (15) and graded according to the Clavien-Dindo classification (16).

2.4 Clinical staging and preoperative treatment

Esophagogastroduodenoscopy with biopsy, CT scan of the cervical, thoracic, and abdominal regions were used for the clinical staging. The evaluation was completed using positron emission tomography (PET/CT) and endoscopic ultrasound (EUS) when deemed necessary. Bronchoscopy was performed in all patients with SCC and in those with possible airways infiltration. The neoadjuvant treatment was not standardized as patients were frequently referred for surgery after being treated at other centers, therefore variations in the chosen regimens could occur based on the preferences of the treating oncologists or the patients' conditions and comorbidities. However, perioperative chemotherapy with FLOT (17) or preoperative chemoradiotherapy with the CROSS scheme (18) were the most frequently used regimens.

2.5 Surgical technique

The surgical techniques used for open esophagectomy (19–21), MIE (22, 23) and RAMIE (24, 25) were previously described. Briefly, all procedures included the mobilization of the stomach and the creation of a gastric conduit in the abdominal part. In the thoracic part, the esophagus was mobilized and transected above the azygos vein. A standard two-field lymphadenectomy was performed (26). The anastomosis was secured using an end-to-side circular-stapled technique. For the open procedure a median laparotomy and a posterolateral or anterolateral right thoracotomy were performed, with the patient in a left lateral decubitus during the thoracic phase. For both MIE and RAMIE, after the abdominal phase the patient was placed in the semi-prone position and the thoracic phase was performed with 4 operative trocars placed along the anterior axillary line (one additional assistant-trocar was used for RAMIE).

All patients were intubated using a left-sided double-lumen tube and a one-lung ventilation was used throughout the thoracic phase. Analgesia was provided by means of an epidural catheter. Postoperative care included early extubation, preferably in the operatory room, epidural- and patient-controlled analgesia, respiratory exercise, and early mobilization and ambulation. After surgery, patients were admitted to the intensive care unit (ICU) and subsequently discharged towards the surgical ward upon confirmation of the hemodynamical and respiratory stability. No enhanced recovery program was used.

2.6 Statistical analysis

All statistical analyses were conducted using GraphPad Prism version 9.2.0 (GraphPad software, San Diego, CA, USA) and JMP version 14 (JMP® software, SAS Institute, Cary, NC, USA). Continuous variables were presented as median (interquartile range [IQR]), prevalence data were presented as raw number (percentage). Comparisons of continuous variables were conducted using the Student's t-test or the Mann-Whitney test. ANOVA or Kruskal Wallis tests were used for multiple comparisons of continuous variables as appropriate. Shapiro-Wilk test was applied to test the normality of the data ($p > 0.10$). Categorical data were compared using the χ^2 or the Fisher's exact test as appropriate. The Bonferroni correction for multiple comparisons was applied when indicated. The threshold for statistical significance was set to $p < 0.05$. For the purpose of randomization, a one-to-one nearest neighbor approach was used for the selection of patients in the matched control group.

3 Results

Clinical characteristics of the studied population are summarized in Table 1. Elderly patients presented with a higher comorbidity index and with a worse physical- ($p < 0.0001$) and performance-status ($p = 0.003$). EAC was the most frequent histology, however a significantly higher proportion of patients in the ≥ 75y group presented with ESCCs ($p = 0.0007$) located in the mid-lower portion of the thoracic esophagus ($p = 0.0003$). Despite no significant difference in the cancer stage at presentation ($p = 0.92$), multimodal treatment comprising chemotherapy or chemoradiotherapy before surgery was less frequently used in elderly patients ($p < 0.0001$) and an open approach rather than a minimally invasive one was preferred in this subgroup ($p < 0.0001$).

Subset analyses of the < 75y group and the ≥ 75y group are reported in Table 2. Within the < 75y group no difference was detected in the patients' clinical characteristics at presentation. Albeit not statistically significant, a higher proportion of patients in the < 75y MI group presented with ESCC (21.2% vs. 14.1%, $p = 0.07$). Among elderly patients, the male sex was prevalent, however, a significantly higher proportion of patients in the ≥ 75y open group was female (31.4% vs. 15.5%, $p = 0.03$). No further difference was detected in the preoperative characteristics of these patients.

Surgical outcomes are depicted in Table 3. The use of a minimally invasive approach in elderly patients did not compromise the surgical radicality of the primary tumor resection ($p = 0.99$) and of the lymph nodes dissection ($p = 0.53$). These results were paralleled by those of the control group. Overall, the proportion of patients experiencing postoperative complications was significantly higher in the ≥ 75y open group compared to the ≥ 75y MI group (62.7% vs. 39.7%, $p = 0.005$). The main determinant of the increased morbidity in the ≥ 75y open group were pulmonary complications, which increased significantly after open surgery (56.9% vs. 32.8%, $p = 0.003$) and consisted mainly of pneumonia (20.6% vs. 8.6%, $p = 0.04$) and mucous plugging requiring bronchoscopy (22.6% vs. 10.3%, $p = 0.05$). Similar results were obtained in the < 75y group: postoperative morbidity (43.5% vs. 31.2%, $p = 0.01$) and pulmonary complication (36% vs. 22%, $p = 0.001$) were significantly higher after open surgery. Pneumonia (11.9% vs. 6%, $p = 0.03$) and mucous plugging (12.4% vs. 7.2%, $p = 0.04$) were the most frequently reported pulmonary complications also in this subgroup.

The incidence and severity of anastomotic leakage did not differ after MI and open surgery within both the < 75y group and ≥ 75y group. Grade 2 leakages were primarily treated by an endoscopically placed nasogastric tube, vacuum-device (EsoSponge®, B. Braun, Melsungen, Germany) or stent and did not require a reoperation. Grade 3 leakages required reoperation with dismantling of the gastric pull-up and cervical esophagostomy.

Overall, 15 patients required reoperation in the ≥ 75y group (9.4%), the main reasons were the presence of a grade 3 leakage (3 patients) or conduit necrosis (3 patients), hemothorax (6 patients), chyle leak (1 patient) and postoperative abdominal bleeding (2 patients). Thirty-one patients required a reoperation in the < 75y group (7.3%). The main causes of reoperation were grade 3 leakage (6 patients) or conduit necrosis (3 patients), hemothorax (16 patients), chyle leak (2 patients), bowel perforation (1 patient) and abdominal bleeding (2 patients). The rate of reoperations, the severity of postoperative complications (Clavien Dindo grade) and the rate of in-hospital mortality were similar after MI or open surgery in both study groups. Patients of the ≥ 75y open group required a longer hospital stay compared to the ≥ 75y MI group ($p = 0.03$).

Table 4 reports the clinical characteristics of the ≥ 75y MI group and the ≥ 75y open group after one-to-one matching for patient's sex, cancer stage and preoperative treatment. The matching resulted in no significant difference in the preoperative variables.

Table 5 summarizes the postoperative outcomes of the two subgroups after the matching. The matched analysis confirmed a significantly higher rate of postoperative complications in the ≥ 75y open group (62.1% vs. 39.7%, $p = 0.02$) with pulmonary complications ($p = 0.04$) being the main determinant of the postoperative morbidity.

Median follow up time was 28 months (10-84). Median overall survival (OS) of the < 75y MI group was 62 months and 49 months in the < 75y open group ($p=0.35$) (Figure 1A). The disease free survival (DFS) of the two groups was also not significantly different (26 vs. 16 months, $p=0.59$) (Figure 1B).

TABLE 1 Clinical characteristic of the studied population.

Variable	< 75y group (N=427)	≥ 75y group (N=160)	p
Median age (years)	61 (55-67)	78 (76-81)	< 0.0001
Sex (N, %)			
Male	356 (83.4)	119 (74.4)	0.01
Female	71 (16.6)	41 (25.6)	
Height (m)	1.76 (1.70-1.80)	1.72 (1.67-1.78)	0.04
Weight (kg)	77 (67.5-88)	74 (65-85.5)	0.12
ASA score (N, %)			
1	5 (1.2)	1 (0.6)	< 0.0001
2	222 (52)	41 (25.6)	
3	194 (45.4)	98 (61.3)	
4	6 (1.4)	20 (12.5)	
Karnofsky performance status (N, %)*			
100-90	380 (89)	125 (78.1)	0.003
80-70	44 (10.3)	33 (20.6)	
60-50	3 (0.7)	2 (1.3)	
Charlson's Comorbidity Index (CCI)	4 (3-5)	6 (5-7)	< 0.0001
Cancer histology (N, %)			
ESCC	78 (18.3)	50 (31.3)	0.0007
EAC	349 (81.7)	110 (68.7)	
Cancer location (N, %)			
Thoracic esophagus	52 (12.2)	41 (25.6)	0.0003
Siewert 1	212 (49.6)	71 (44.4)	
Siewert 2	163 (38.2)	48 (30)	
cTNM Staging			
Stage 1	39 (9.1)	13 (8.1)	0.92
Stage 2	88 (20.6)	31 (19.4)	
Stage 3	273 (63.9)	104 (65)	
Stage 4	27 (6.4)	12 (7.5)	
Perioperative treatment (N, %)			
None	67 (15.7)	96 (60)	< 0.0001
Chemotherapy	168 (39.3)	33 (20.6)	
Chemoradiotherapy	190 (44.5)	29 (18.1)	
Radiotherapy	2 (0.5)	2 (1.3)	
Surgical approach (N, %)			
Open	178 (41.7)	102 (63.7)	< 0.0001
Laparoscopic/Thoracoscopic (MIE)	94 (22)	24 (15)	
Fully Robotic (RAMIE)	155 (36.3)	34 (21.3)	

TABLE 2 Clinical characteristics of the analyzed subgroups.

Variable	< 75y MI group (N=250)	< 75y open group (N=177)	p	≥ 75y MI group (N=58)	≥ 75y open group (N=102)	p
Median age (years)	61 (55-68)	60 (53-67)	0.28	79 (76-82)	77 (76-80)	0.51
Sex (N, %)						
Male	205 (82)	151 (85.3)	0.37	49 (84.5)	70 (68.6)	0.03
Female	45 (18)	26 (14.7)		9 (15.5)	32 (31.4)	
Height (m)	1.76 (1.65-1.79)	1.77 (1.71-1.80)	0.42	1.72 (1.67-1.78)	1.70 (1.58-1.75)	0.28
Weight (kg)	77 (68-88)	79 (69-91)	0.33	74 (65.5-86)	72 (59-81.5)	0.53
ASA score (N, %)						
1	3 (1.2)	2 (1.1)	0.13	0	1 (0.9)	0.87
2	119 (47.6)	103 (58.2)		15 (25.9)	26 (25.5)	
3	123 (49.2)	71 (40.1)		35 (60.3)	63 (61.8)	
4	5 (2)	1 (0.6)		8 (13.8)	12 (11.8)	
Karnofsky performance status (N, %)						
100-90	219 (87.6)	161 (91)	0.26	45 (77.6)	80 (78.5)	0.92
80-70	28 (11.2)	16 (9)		12 (20.7)	21 (20.6)	
60-50	3 (1.2)	0		1 (1.7)	1 (0.9)	
Charlson's Comorbidity Index (CCI)	5 (3.5-6.5)	4 (3-5)	0.15	5 (3-7)	6 (5-7)	0.28
Cancer histology (N, %)						
ESCC	53 (21.2)	25 (14.1)	0.07	18 (31)	32 (31.4)	0.96
EAC	197 (78.8)	152 (85.9)		40 (69)	70 (68.6)	
Cancer location (N, %)						
Thoracic esophagus	30 (12)	22 (12.4)	0.37	11 (19)	30 (29.4)	0.25
Siewert 1	131 (52.4)	81 (45.8)		26 (44.8)	45 (44.1)	
Siewert 2	89 (35.6)	74 (41.8)		21 (36.2)	27 (26.5)	
cTNM Staging						
Stage 1	29 (11.6)	10 (5.6)	0.17	6 (10.3)	7 (6.9)	0.71
Stage 2	51 (20.4)	37 (20.9)		9 (15.5)	22 (21.6)	
Stage 3	153 (61.2)	120 (67.8)		39 (67.2)	65 (63.7)	
Stage 4	17 (6.8)	10 (5.6)		4 (7)	8 (7.8)	
Perioperative treatment (N, %)						
None	43 (17.2)	24 (13.6)	0.40	31 (53.5)	65 (63.8)	0.29
Chemotherapy	103 (41.2)	65 (36.7)		13 (22.4)	20 (19.6)	
Chemoradiotherapy	103 (41.2)	87 (49.1)		14 (24.1)	15 (14.7)	
Radiotherapy	1 (0.4)	1 (0.6)		0	2 (1.9)	

(Continued)

TABLE 2 Continued

Variable	< 75y MI group (N=250)	< 75y open group (N=177)	p	≥ 75y MI group (N=58)	≥ 75y open group (N=102)	p
Surgical approach (N, %)						
Laparoscopic/ Thoracoscopic (MIE)	95 (38)	–	–	24 (41.4)	–	–
Fully Robotic (RAMIE)	155 (62)	–		34 (58.6)	–	
Operative time (min)	331 (289-380)	285 (245-331)	0.02	340 (310-377)	298 (243-334)	0.03

"-" means the variable in the row is not applicable to the patients in the column.

TABLE 3 Surgical outcomes of the analyzed subgroups.

Variable	< 75y MI group (N=250)	< 75y open group (N=177)	p	≥ 75y MI group (N=58)	≥ 75y open group (N=102)	p
Surgical radicality (N, %)						
R0	245	173	0.99	56	99	0.99
R1	5	4		2	3	
Harvested lymph nodes (N, IQR)	31 (23-40)	28 (20-35)	0.68	27 (19-33)	25 (17-31)	0.53
Metastatic lymph nodes (N, IQR)	2 (0-3)	2 (0-3)	0.28	2 (0-3)	1 (0-4)	0.33
Intraoperative complications (N, %)	8 (3.2)	5 (2.8)	0.82	4 (6.9)	5 (4.9)	0.72
Postoperative morbidity (N, %)	78 (31.2)	77 (43.5)	0.01	23 (39.7)	64 (62.7)	0.005
Anastomotic leakage (N, %)	26 (10.4)	15 (8.4)	0.51	7 (12)	15 (14.6)	0.64
Grade 1	2 (0.8)	1 (0.5)	0.97	1 (1.7)	1 (0.9)	0.83
Grade 2	20 (8)	12 (6.8)		5 (8.6)	12 (11.8)	
Grade 3	4 (1.6)	2 (1.1)		1 (1.7)	2 (1.9)	
Conduit necrosis (N, %)	1 (0.4)	2 (1.1)	0.57	1 (1.7)	2 (1.9)	0.99
Chyle leak (N, %)	8 (3.2)	3 (1.7)	0.54	3 (5.2)	4 (3.9)	0.70
Vocal cord palsy (N, %)	3 (1.2)	2 (1.1)	0.99	0	4 (3.9)	0.29
Hemothorax (N,%)	8 (3.2)	12 (6.8)	0.08	1 (1.7)	6 (5.9)	0.42
Pulmonary complications (N, %)*	55 (22)	64 (36)	0.001	19 (32.8)	58 (56.9)	0.003
Pneumonia	15 (6)	21 (11.9)	0.03	5 (8.6)	21 (20.6)	0.04
Atelectasis mucous plugging requiring bronchoscopy	18 (7.2)	22 (12.4)	0.04	6 (10.3)	23 (22.6)	0.05
Pneumothorax	7 (2.8)	7 (3.9)	0.59	1 (1.7)	4 (3.9)	0.65
Pleural effusion requiring drainage	7 (2.8)	5 (2.8)	0.99	2 (3.4)	5 (4.9)	0.99
Respiratory failure requiring reintubation	5 (2)	6 (3.4)	0.37	3 (5.2)	4 (3.9)	0.70
ARDS	3 (1.2)	3 (1.7)	0.69	0	1 (0.9)	0.99
Cardiac complications (N,%)*	19 (7.6)	17 (9.4)	0.46	6 (10.3)	10 (9.8)	0.91

(Continued)

TABLE 3 Continued

Variable	< 75y MI group (N=250)	< 75y open group (N=177)	p	≥ 75y MI group (N=58)	≥ 75y open group (N=102)	p
Atrial dysrhythmia requiring treatment	11 (4.4)	12 (6.8)	0.28	4 (6.9)	5 (4.9)	0.72
Congestive heart failure requiring treatment	8 (3.2)	5 (2.8)	0.99	2 (3.4)	4 (3.9)	0.99
Myocardial infarction	0	0	0.99	0	1 (0.9)	0.99
Gastrointestinal complications (N,%)*	7 (2.8)	9 (5.1)	0.22	1 (1.7)	4 (3.9)	0.65
Clostridium difficile infection	1 (0.4)	2 (1.1)	0.57	1 (1.7)	3 (2.9)	0.99
Liver dysfunction	1 (0.4)	1 (0.5)	0.99	0	1 (0.9)	0.99
Sepsis	5 (2)	6 (3.4)	0.37	2 (3.4)	11 (10.8)	0.10
Complications: severity[b] (N, %)						
1	6 (2.4)	8 (4.5)	0.88	1 (1.7)	3 (2.9)	0.87
2	23 (9.2)	20 (11.3)		5 (8.6)	10 (9.8)	
3a	19 (7.6)	16 (9)		6 (8.6)	26 (25.5)	
3b	11 (4.4)	12 (6.8)		3 (5.2)	8 (7.8)	
4	14 (5.6)	18 (10.2)		6 (8.6)	12 (11.8)	
5	5 (2)	3 (1.6)		2 (3.4)	5 (4.9)	
Need for reoperation (N, %)	15 (6)	16 (9)	0.23	4 (6.9)	11 (10.8)	0.43
ICU readmission (N, %)	18 (7.2)	21 (11.9)	0.09	7 (12.1)	17 (16.7)	0.49
Length of hospital stay (days) (N, IQR)	12 (10-17)	12 (10-18)	0.19	13 (11-19)	18 (13-26)	0.03
In-hospital mortality (N, %)	5 (2)	3 (1.6)	0.99	2 (3.4)	5 (4.9)	0.99

*The most severe complication for each category is indicated.
[b] According to the Clavien-Dindo classification.

TABLE 4 Clinical characteristics of the analyzed subgroups after matching.

Variable	≥ 75y MI group (N=58)	≥ 75y open group (N=58)	p
Median age (years)	79 (76-82)	78 (75-82)	0.43
Sex (N, %)			
Male	49 (84.5)	50 (86.2)	0.79
Female	9 (15.5)	8 (13.8)	
Height (m)	1.72 (1.67-1.78)	1.71 (1.60-1.76)	0.16
Weight (kg)	74 (65.5-86)	70 (55-78.3)	0.12
ASA score (N, %)			
1	0	1 (1.7)	0.74
2	15 (25.9)	13 (22.4)	
3	35 (60.3)	37 (63.8)	
4	8 (13.8)	7 (12.1)	

(Continued)

TABLE 4 Continued

Variable	≥ 75y MI group (N=58)	≥ 75y open group (N=58)	p
Karnofsky performance status (N, %)			
100-90	45 (77.6)	45 (77.6)	0.59
80-70	12 (20.7)	13 (22.4)	
60-50	1 (1.7)	0	
Charlson's Comorbidity Index (CCI)	5 (3-7)	5 (4-7)	0.72
Cancer histology (N, %)			
ESCC	18 (31)	19 (32.8)	0.84
EAC	40 (69)	39 (67.2)	
Cancer location (N, %)			
Thoracic esophagus	11 (19)	13 (22.4)	0.90
Siewert 1	26 (44.8)	25 (43.1)	
Siewert 2	21 (36.2)	20 (34.5)	
cTNM Staging			
Stage 1	6 (10.3)	7 (12.1)	0.75
Stage 2	9 (15.5)	12 (20.7)	
Stage 3	39 (67.2)	37 (63.8)	
Stage 4	4 (7)	2 (3.4)	
Perioperative treatment (N, %)			
None	31 (53.5)	29 (50)	0.81
Chemotherapy	13 (22.4)	16 (27.6)	
Chemoradiotherapy	14 (24.1)	13 (22.4)	
Radiotherapy	0	0	

TABLE 5 Surgical outcomes of the analyzed subgroups after matching.

Variable	≥ 75y MI group (N=58)	≥ 75y open group (N=58)	p
Surgical radicality (N, %)			
R0	56	57	0.99
R1	2	1	
Harvested lymph nodes (N, IQR)	27 (19-33)	26 (16-32)	0.48
Metastatic lymph nodes (N, IQR)	2 (0-3)	1 (0-4)	0.60
Intraoperative complications (N, %)	4 (6.9)	2 (3.4)	0.68
Postoperative morbidity (N, %)	23 (39.7)	36 (62.1)	0.02
Anastomotic leakage (N, %)	7 (12.1)	5 (8.6)	0.76
Grade 1	1 (1.7)	1 (1.7)	0.92
Grade 2	5 (8.6)	3 (5.2)	

(Continued)

TABLE 5 Continued

Variable	≥ 75y MI group (N=58)	≥ 75y open group (N=58)	p
Grade 3	1 (1.7)	1 (1.7)	
Conduit necrosis (N, %)	1 (1.7)	0	0.99
Chyle leak (N, %)	3 (5.2)	1 (1.7)	0.62
Vocal cord palsy (N, %)	0	1 (1.7)	0.99
Hemothorax (N,%)	1 (1.7)	4 (6.9)	0.36
Pulmonary complications (N,%)*	19 (32.8)	30 (51.7)	0.04
Pneumonia	5 (8.6)	12 (20.7)	0.07
Atelectasis mucous plugging requiring bronchoscopy	6 (10.3)	15 (25.9)	0.03
Pneumothorax	1 (1.7)	0	0.99
Pleural effusion requiring drainage	2 (3.4)	2 (3.4)	0.99
Respiratory failure requiring reintubation	3 (5.2)	1 (1.7)	0.62
ARDS	0	0	0.99
Cardiac complications (N,%)*	6 (10.3)	5 (8.6)	0.99
Atrial dysrhythmia requiring treatment	4 (6.9)	3 (5.2)	0.99
Congestive heart failure requiring treatment	2 (3.4)	2 (3.4)	0.99
Myocardial infarction	0	0	0.99
Gastrointestinal complications (N,%)*	1 (1.7)	1 (1.7)	0.99
Clostridium difficile infection	1 (1.7)	1 (1.7)	0.99
Liver dysfunction	0	0	0.99
Sepsis	2 (3.4)	6 (10.3)	0.27
Complications: severity[b] (N, %)			
1	1 (1.7)	1 (1.7)	0.92
2	5 (8.6)	9 (15.5)	
3a	6 (8.6)	12 (20.7)	
3b	3 (5.2)	4 (6.9)	
4	6 (8.6)	9 (15.5)	
5	2 (3.4)	1 (1.7)	
Need for reoperation (N, %)	4 (6.9)	6 (10.3)	0.51
ICU readmission (N, %)	7 (12.1)	10 (17.2)	0.43
Length of hospital stay (days)(N, IQR)	13 (11-19)	15 (11-20)	0.09
In-hospital mortality (N, %)	2 (3.4)	1 (1.7)	0.99

* The most severe complication for each cathegory is indicated.
[b] According to the Clavien-Dindo classification.

No difference was detected in the OS of the ≥ 75y MI group (26 months) and the ≥ 75y open group (19 months)(p=0.84) (Figure 2A). The DFS was also similar between the two groups (26 months vs. 13 months, p=0.25) (Figure 2B).

4 Discussion

In this multicentric cohort study, the use of a minimally invasive approach improved the postoperative outcome of elderly

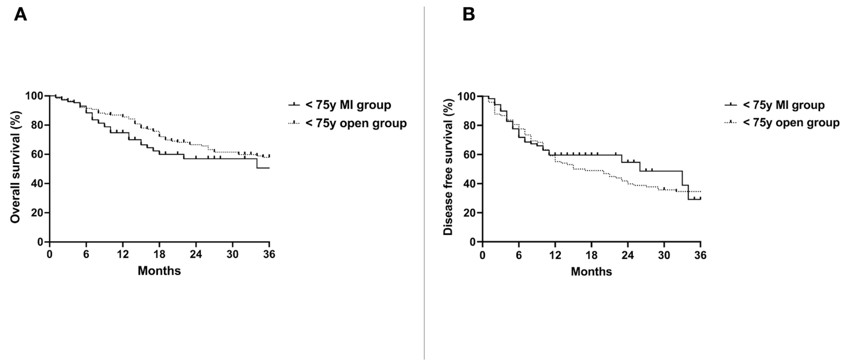


FIGURE 1
Overall survival **(A)** and disease free survival **(B)** of the < 75y MI group vs. the < 75y open group. Whole cohort.

patients undergoing Ivor Lewis esophagectomy by significantly reducing the rate of pulmonary complications, particularly of pneumonia and mucous plugging causing atelectasis. This translated into a significantly shorter hospital stay. Although not significantly, the rate of ICU re-admission and reoperation were also decreased after MIE/RAMIE. The results were confirmed at the one-to-one matched univariate analysis of the elderly group, moreover, similar outcomes were reported in the control group comprising younger patients.

Esophagectomy is a complex procedure, the rate of postoperative morbidity reported in the literature ranges widely between 20% and 80% (1, 2) while postoperative mortality ranges from 0% to 22% (1, 3). This seems to correspond to a higher postoperative morbidity and mortality rate in elderly patients compared to the younger ones (27). In a 2013 meta-analysis, Markar et al. reported an increased risk of pulmonary (21.8%) and cardiac complications (18.7%) after esophagectomy for patients > 70 years-old, with a 2 fold increase in the risk of postoperative death (7.8%) and a reduced cancer-related 5-year survival (21.2%) (28). Similarly, Schlottmann et al. reported that the predicted probability of mortality increased consistently across age (2.5% in 50 years, 5.4% in 70 years and 7% in 80) (29). These findings are understandable, since elderly patients represent a fragile subset often presenting in worse baseline clinical conditions and, consequently, with reduced reserves and capacity to endure major surgical procedures (1, 30). In our cohort, the ≥ 75y group presented with a significantly worse performance status and a higher comorbidity index compared to the control group. The overall in-hospital mortality of the elderly group was indeed higher, although not significantly, compared to the < 75y patients (4.4% vs. 1.9%, $p = 0.09$). However, this mortality rate doesn't seem to be prohibitive, if we consider that the currently published benchmarks for mortality after esophagectomy performed in optimal conditions (i.e. in healthy patients and referral centers) range between 2.3% and 5.1% (1, 31).

Minimally invasive esophagectomy has been introduced in the last decades with the aim of reducing the surgical trauma, the complications and improving the quality of life after surgery. Currently, 4 randomized controlled trials comparing hybrid- (32), totally-minimally invasive esophagectomy (4, 33) and RAMIE (5) to open surgery demonstrated a reduction in overall postoperative complications and pulmonary complications. In this context, the use of a minimally invasive approach might seem particularly beneficial in the elderly population, which is more prone to the

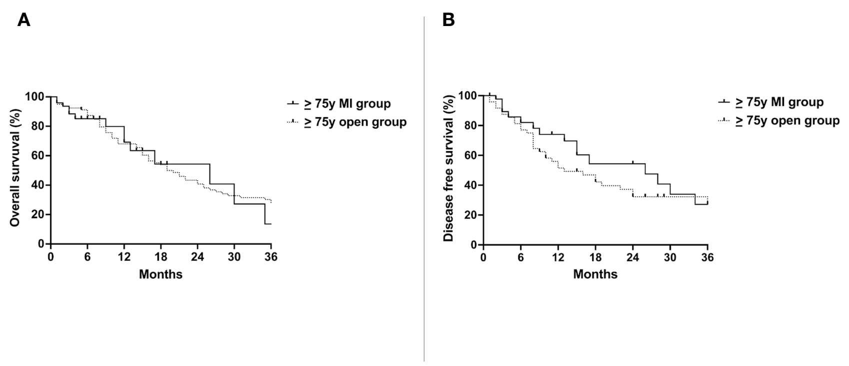


FIGURE 2
Overall survival **(A)** and disease free survival **(B)** of the ≥ 75y MI group vs. the ≥ 75y open group. Whole cohort.

inherent morbidity of open esophagectomy. However, the matter is more controversial if we consider two factors. First, the reported outcomes of minimally invasive esophagectomy are not uniformly favorable in the published literature: the TIME trial showed an almost two-fold increase of the anastomotic leakage rate after MIE compared to the open approach (12% vs. 7%) (4). Similarly, in the large population-based study from the Dutch Upper Gastrointestinal Cancer Audit (DUCA) (34) the anastomotic leak and the reintervention rates were higher after MIE (21.2% vs. 15.5% and 28.2% vs. 21.1% respectively). This is particularly relevant considering that the leakage-related mortality has been reported to be up to 8.5 time higher in elderly patients compared to the younger ones (35). Second, several authors still found significantly higher pulmonary complications and mortality rates among elderly patients despite being operated without a trans-thoracic approach (35–37). Therefore, the actual benefit of using thoracoscopy for the thoracic phase might be limited. Taken together, these findings may question the benefit of using MIE or RAMIE in elderly patients.

Several studies compared the outcomes of minimally invasive esophagectomy between cohorts of elderly and non-elderly patients, reporting less cardiovascular complications (7), anastomotic leakages (8) and a reduced 90-day mortality (9) among younger patients. However, the literature directly comparing different surgical approaches for esophagectomy in the elderly population is somewhat limited. In a retrospective cohort study from 2015, Li et al. (10) analyzed the postoperative outcomes of 407 patients older than 70 years who underwent either MIE or open esophagectomy. After paired matching of 116 patients (58 pairs) the authors reported a significantly reduced rate of postoperative complications, particularly of pulmonary complications, with a shorter hospital stay and a reduced need for ICU readmission after MIE. In this series, however, 96.6% of patients in the MIE group underwent McKeown esophagectomy with cervical anastomosis, therefore the results are hardly applicable to the Western clinical practice, were intra-thoracic anastomoses are more frequently performed (38).

The effect of using a minimally invasive approach on the incidence of postoperative leakage after Ivor Lewis is still unclear (4, 34). Given the higher leakage-associated mortality among elderly patients (35), whether it is beneficial to perform MIE-Ivor Lewis in an elderly subject remains an unanswered question. To the best of our knowledge, our case series is one of the largest addressing this issue, by directly comparing the outcome of minimally invasive and open Ivor Lewis esophagectomy in the elderly.

In our study, the minimally invasive approach proved not only to be feasible in ≥ 75 years-old-patients, but also effective in improving the postoperative course by reducing postoperative complications. A significant reduction in pulmonary complications was the main determinant of the final outcome and this is coherent with the results reported in most of the currently available cohort studies (6) and the TIME trial (4). Even more interestingly, in our study more than half of the patients in the ≥ 75y MI group were operated using RAMIE (58.6%), thus confirming the feasibility and safety of this approach for healthy subjects. Prior to our study the evidence regarding the use of RAMIE in elderly subjects was rather limited considering that the mean age of the robotic-cohort in the ROBOT trial was 64 years (5).

The presence of a bias due to the *a priori* selection of elderly patients in better overall condition and performance status for MIE/RAMIE rather than open surgery might be a limit of this study. This might explain the significant differences in the clinical characteristics of elderly patients at presentation (cancer histology, location, and stage) that was detected in our cohort. Another issue might be the relatively small sample size of the ≥ 75y MI group compared to the open one. However, the fact that the results were confirmed after matching our cohort and that the control group showed a similar trend in the postoperative course seems to ascertain the benefit provided by the minimally invasive approach in our series.

The multicentric design of this study and the inclusion of both MIE and RAMIE cases might also be a limitation since technical differences between the two approaches and the two recruiting centers should be accounted for. However, we believe that this aspect had a limited impact on our results since the operative setting and the key surgical steps of the two procedures, particularly the end-to-side circular-stapled anastomosis, were practically identical and the same anastomotic technique was also used for the open-cases.

Finally, we decided to use a cutoff value of 75 years of age to define elderly patients, while other studies used other cutoffs, e.g. 70 years (10, 28). The definition of elderly patients is indeed rather variable in the literature. However, esophageal cancer is most frequently diagnosed among people aged 65 to 74 years, the median age at diagnosis being 68 years. Indeed, according to NIH data, the percentage of new cases is highest in the 65-to-74-year age group, reaching 33.3% (39).

For these reasons, considering the aim of the study, we believe it would've been misleading to use a lower cutoff value to define "elderly patients with esophageal cancer" (such as 60 or 70 years). Such a subgroup (> 60 years or > 70 years patients) wouldn't in fact be representative of a group of elderly esophageal-cancer patients, but rather of the average-aged esophageal cancer patient.

Nevertheless, we obtained the same results reported in the study even conducting a separate analysis using > 70 years as a cutoff (see Supplementary Material).

5 Conclusions

The use of a minimally invasive approach for Ivor Lewis esophagectomy, including the robotic approach, is feasible and safe in elderly patients, even though this subset of patients usually presents in a worse clinical condition and with a poor performance status. Compared to open surgery, the improvement in terms of reduction of postoperative complications, particularly pulmonary complications, is comparable between elderly and younger patients. The surgical radicality and the incidence of procedure-specific complications (anastomotic leakage, conduit necrosis, chyle leak etc.) is comparable between the two procedures in both age-groups.

Data availability statement

The raw data supporting the conclusions of this article can be made available by the authors under reasonable request to the corresponding author at lucia.moletta@unipd.it.

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

Study conception and design: GC, EU, LM, EH, EP, GZ, ET, FB, HL, MV, and PG; Acquisition of data: GC, EU, AS, LM, EH, LP, RS, EP, GZ, ET, and FB; Analysis and interpretation of data: GC, EU, LM, EH, LP, RS, ET, FB, HL, MV, and PG; Drafting of manuscript: GC, EU, AS, LM, and EH; Critical revision: LP, RS, EP, GZ, ET, FB, HL, MV, and PG. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1104109/full#supplementary-material

References

1. Raymond DP, Seder CW, Wright CD, Magee MJ, Kosinski AS, Cassivi SD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a society of thoracic surgeons general thoracic surgery database risk adjustment model. *Ann Thorac Surg* (2016) 102(1):207. doi: 10.1016/j.athoracsur.2016.04.055

2. Morita M, Nakanoko T, Fujinaka Y, Kubo N, Yamashita N, Yoshinaga K, et al. In-hospital mortality after a surgical resection for esophageal cancer: analyses of the associated factors and historical changes. *Ann Surg Oncol* (2011) 18(6):1757–65. doi: 10.1245/s10434-010-1502-5

3. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. *J Gastrointest Surg* (2012) 16(5):1055–63. doi: 10.1007/s11605-011-1731-3

4. Biere SSAY, Van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* (2012) 379(9829):1887–92. doi: 10.1016/S0140-6736(12)60516-9

5. van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. *Ann Surg* (2019) 269(4):621–30. doi: 10.1097/SLA.0000000000003031

6. Van Der Sluis PC, Schizas D, Liakakos T, Van Hillegersberg R. Minimally invasive esophagectomy. *Dig Surg* (2020) 37(2):93–100. doi: 10.1159/000497456

7. Baranov NS, van Workum F, van der Maas J, Kouwenhoven E, van Det M, van den Wildenberg FJH, et al. The influence of age on complications and overall survival after ivor Lewis totally minimally invasive esophagectomy. *J Gastrointest Surg* (2019) 23 (7):1293–300. doi: 10.1007/s11605-018-4062-9

8. Sugita Y, Nakamura T, Sawada R, Takiguchi G, Urakawa N, Hasegawa H, et al. Safety and feasibility of minimally invasive esophagectomy for elderly esophageal cancer patients. *Dis esophagus Off J Int Soc Dis Esophagus* (2021) 34(3):1–7. doi: 10.1093/dote/doaa083

9. Hol JC, Heisterkamp J, Martijnse IS, Matthijsen RA, Langenhoff BS. Morbidity and mortality in elderly patients after minimally invasive esophagectomy. *Ann Esophagus* (2019) 2(0):3–9. doi: 10.21037/aoe.2019.03.01

10. Li J, Shen Y, Tan L, Feng M, Wang H, Xi Y, et al. Is minimally invasive esophagectomy beneficial to elderly patients with esophageal cancer? *Surg Endosc* (2015) 29(4):925–30. doi: 10.1007/s00464-014-3753-x

11. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* (2017) 6(2):119–30. doi: 10.21037/acs.2017.03.14

12. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* (1984) 2(3):187–93. doi: 10.1200/JCO.1984.2.3.187

13. Saklad M. GRADING OF PATIENTS FOR SURGICAL PROCEDURES. *Anesthesiology* (1941) 2(3):281–4. doi: 10.1097/00000542-194105000-00004

14. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* (1994) 47(11):1245–51. doi: 10.1016/0895-4356(94)90129-5

15. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). *Ann Surg* (2015) 262(2):286–94. doi: 10.1097/SLA.0000000000001098

16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae

17. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* (2016) 17(12):1697–708. doi: 10.1016/S1470-2045(16)30531-9

18. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* (2012) 366(22):2074–84. doi: 10.1056/NEJMoa1112088

19. Ruol A, Portale G, Castoro C, Merigliano S, Cagol M, Cavallin F, et al. Effects of neoadjuvant therapy on perioperative morbidity in elderly patients undergoing

esophagectomy for esophageal cancer. *Ann Surg Oncol* (2007) 14(11):3243–50. doi: 10.1245/s10434-007-9455-z

20. Ruol A, Castoro C, Portale G, Cavallin F, Silent VC, Cagol M, et al. Trends in management and prognosis for esophageal cancer surgery: twenty-five years of experience at a single institution. *Arch Surg* (2009) 144(3):247–54. doi: 10.1001/archsurg.2008.574

21. Hölscher AH, Schröder W, Bollschweiler E, Beckurts KTE, Schneider PM. [How safe is high intrathoracic esophagogastrostomy?]. *Chirurg* (2003) 74(8):726–33. doi: 10.1007/s00104-003-0649-z

22. Valmasoni M, Capovilla G, Pierobon ES, Moletta L, Provenzano L, Costantini M, et al. A technical modification to the circular stapling anastomosis technique during minimally invasive ivor Lewis procedure. *J Laparoendosc Adv Surg Tech A* (2019) 29 (12):1585–91. doi: 10.1089/lap.2019.0461

23. Froiio C, Uzun E, Hadzijusufovic E, Capovilla G, Berlth F, Lang H, et al. Semiprone thoracoscopic approach during totally minimally invasive ivor-Lewis esophagectomy seems to be beneficial. *Dis Esophagus* (2022) 36:1–11. doi: 10.1093/dote/doac044/6627608

24. Grimminger PP, Hadzijusufovic E, Babic B, van der Sluis PC, Lang H. Innovative fully robotic 4-arm ivor Lewis esophagectomy for esophageal cancer (RAMIE4). *Dis Esophagus* (2020) 33(3):1–4. doi: 10.1093/dote/doz015

25. van der Sluis PC, Tagkalos E, Hadzijusufovic E, Babic B, Uzun E, van Hillegersberg R, et al. Robot-assisted minimally invasive esophagectomy with intrathoracic anastomosis (Ivor lewis): promising results in 100 consecutive patients (the European experience). *J Gastrointest Surg* (2021) 25(1):1–8. doi: 10.1007/s11605-019-04510-8

26. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* (1994) 220(3):364. doi: 10.1097/00000658-199409000-00012

27. Mantziari S, Farinha HT, Bouygues V, Vignal JC, Deswysen Y, Demartines N, et al. Esophageal cancer in elderly patients, current treatment options and outcomes; a systematic review and pooled analysis. *Cancers* (2021) 13(9):2104–24. doi: 10.3390/cancers13092104

28. Markar SR, Karthikesalingam A, Thrumurthy S, Ho A, Muallem G, Low DE. Systematic review and pooled analysis assessing the association between elderly age and outcome following surgical resection of esophageal malignancy. *Dis esophagus Off J Int Soc Dis Esophagus* (2013) 26(3):250–62. doi: 10.1111/j.1442-2050.2012.01353.x

29. Schlottmann F, Strassle PD, Nayyar A, Herbella FAM, Cairns BA, Patti MG. Postoperative outcomes of esophagectomy for cancer in elderly patients. *J Surg Res* (2018) 229:9–14. doi: 10.1016/j.jss.2018.03.050

30. Johansson J, Walther B. Clinical outcome and long-term survival rates after esophagectomy are not determined by age over 70 years. *J Gastrointest Surg* (2000) 4 (1):55–62. doi: 10.1016/S1091-255X(00)80033-5

31. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. *Ann Surg* (2019) 269(2):291–8. doi: 10.1097/SLA.0000000000002611

32. Mariette C, Markar SR, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al. Hybrid minimally invasive esophagectomy for esophageal cancer. *N Engl J Med* (2019) 380(2):152–62. doi: 10.1056/NEJMoa1805101

33. Ma G, Cao H, Wei R, Qu X, Wang L, Zhu L, et al. Comparison of the short-term clinical outcome between open and minimally invasive esophagectomy by comprehensive complication index. *J Cancer Res Ther* (2018) 14(4):789–94. doi: 10.4103/jcrt.JCRT_48_18

34. Seesing MFJ, Gisbertz SS, Goense L, Van Hillegersberg R, Kroon HM, Lagarde SM, et al. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. *Ann Surg* (2017) 266(5):839–46. doi: 10.1097/SLA.0000000000002393

35. Schweigert M, Solymosi N, Dubecz A, Stadlhuber RJ, Ofner D, Stein HJ. Current outcome of esophagectomy in the very elderly: experience of a German high-volume center . *Am Surg* (2013) 79(8):754–63. doi: 10.1177/000313481307900814

36. Ma JY, Wu Z, Wang Y, Zhao YF, Liu LX, Kou YL, et al. Clinicopathologic characteristics of esophagectomy for esophageal carcinoma in elderly patients. *World J Gastroenterol* (2006) 12(8):1296–9. doi: 10.3748/wjg.v12.i8.1296

37. Takagawa R, Kunisaki C, Makino H, Oshima T, Nagano Y, Fujii S, et al. Therapeutic management of elderly patients with esophageal cancer. *Esophagus* (2008) 53:133–9. doi: 10.1007/s10388-008-0159-7

38. Voeten DM, Gisbertz SS, Ruurda JP, Wilschut JA, Ferri LE, Van Hillegersberg R, et al. Overall volume trends in esophageal cancer surgery results from the Dutch upper gastrointestinal cancer audit. *Ann Surg* (2022) 274(3):449–58. doi: 10.1097/SLA.0000000000004985

39. National Cancer Institute. *Surveillance, epidemiology, and end results program* Available at: https://seer.cancer.gov/statfacts/html/esoph.html (Accessed April 18, 2023).