Liver Resection for Colorectal Liver-limited Metastases in Elderly Patients: A Propensity Score Matching Analysis

Ke-Min Jin  
Beijing Cancer Hospital

Kun Wang  
Beijing Cancer Hospital

Quan Bao  
Beijing Cancer Hospital

Hong-Wei Wang  
Beijing Cancer Hospital

Bao-Cai Xing (xingbaocai88@sina.com)  
Peking University School of Oncology

Research

Keywords: Liver-limited metastases, Colorectal cancer, Elderly, Hepatectomy, Survival

DOI: https://doi.org/10.21203/rs.3.rs-53989/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Few studies have focused on the role of hepatectomy for colorectal liver-limited metastases in elderly patients compared to matched younger patients.

**Methods:** From January 2000 to December 2018, 724 patients underwent hepatectomy for colorectal liver-limited metastases. Based on a 1:2 propensity score matching (PSM) model, 64 elderly patients (≥ 70 years of age) were matched to 128 younger patients (< 70 years of age) to obtain two balanced groups with regards to demographic, therapeutic and prognostic factors.

**Results:** There were 73 elderly and 651 younger patients in the unmatched cohort. Compared with the younger group (YG), the elderly group (EG) had significantly higher proportion of American Society of Anesthesiologists score and comorbidities, and lower proportion of more than 3 liver metastases and postoperative chemotherapy (p < 0.05). After PSM for these factors, rat sarcoma virus proto-oncogene/B-Raf proto-oncogene (RAS/BRAF) mutation status and primary tumor sidedness, the EG had significantly less median intraoperative blood loss than the YG (175 ml vs. 200 ml, p = 0.046), a shorter median postoperative hospital stay (8 days vs. 11 days, p = 0.020) and a higher readmission rate (4.7% vs. 0%, p = 0.036). The EG also had longer disease-free survival (DFS), overall survival (OS) and cancer-specific survival (CSS) compared to the YG, but these findings were not statistically significant (p > 0.05). Old age was not an independent factor for DFS, OS and CSS by Cox multivariate regression analysis (p > 0.05).

**Conclusions:** Hepatectomy is safe for colorectal liver-limited metastases in elderly patients, and these patients may subsequently benefit from prolonged DFS, OS and CSS.

**Background**

In 2018, colorectal cancer had the third greatest incidence and the second greatest mortality of all malignant tumors [1]. Approximately half of all colorectal cancer patients have disease that eventually progresses to synchronous or metachronous liver metastases (LM) with or without extrahepatic diseases (EHD) [2, 3]. Radical resection of all liver metastases is the mainstay of management for these patients, which has lead to 5-year survival rates of 36–58% [4–9]. However, with the aging of the global population, an increasing number of patients are being diagnosed at an elderly age, when resection may not be a viable treatment option due to a patient’s poor performance status or comorbidities [10]. For the elderly patients who do undergo hepatectomy, there have been conflicting results of studies regarding operation safety and long-term survival [11–19]. These studies were not conclusive in part due to biased or missing baseline data, comorbidities, the American Society of Anesthesiologists (ASA) score, and preoperative treatment in these studies. To the best of our knowledge, only one study using the propensity score matching method has been published, which demonstrated comparable short-term and long-term outcomes between the younger group (YG) and the elderly group (EG) [20].

Another flaw of these studies, which investigated the justification for liver resection for colorectal liver metastases in elderly patients, is that they did include patients with EHD. Furthermore, most of the studies
did not elaborate on the type and/or management of the EHDs, which could potentially hinder accurate evaluation of disease-free survival. In modern management of colorectal liver metastases, important data such as primary sidedness, RAS/BRAF mutation status, preoperative chemotherapy and clinical risk score (CRS) were not included in the analyses. The present study was designed to elucidate the role of hepatectomy in elderly patients with colorectal liver-limited metastases using a propensity score matching analysis to overcome the aforementioned limitations of previous work.

**Methods**

**Data Collection**

Data from patients with colorectal liver-limited metastases who underwent complete resection of hepatic metastases between January 2000 and December 2018 at the Hepatobiliary and Pancreatic Surgery Unit I of Beijing Cancer Hospital were retrospectively collected. The study was approved by the hospital's Clinical Research Ethics Committee and was performed in compliance with the Helsinki Declaration. Patients with a second primary malignant tumor were excluded. Only the first operation was included for patients who underwent a repeat hepatectomy for disease recurrence. For patients who underwent complete resection by two-stage hepatectomy (portal vein ligation or embolization), only the second surgery – the high-risk right hemi-liver resection – was included. All tumor tissues resected prior to 2015 were retrieved and sent for retrospective RAS/BRAF mutation analysis. The following patient information was evaluated: (1) demographic features, comorbidities and ASA score; (2) primary tumor sidedness, T stage and N stage; (3) number, distribution and maximum diameter of liver metastases; (4) preoperative serum levels of the tumor marker carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9), temporal relationship of primary tumor and liver metastases, preoperative CRS, preoperative chemotherapy and RAS/BRAF mutation status; (5) operation time, procedural details (major hepatectomy, combination with radiofrequency ablation (RFA), simultaneous resection, Pringle clamping time of the hepaticoduodenal ligament), intraoperative blood loss and red blood cell (RBC) transfusion and margin status; (6) postoperative hospital stay, postoperative general and surgical complications; (7) postoperative adjuvant chemotherapy protocol and history of repeat hepatectomy after recurrence; (8) postoperative follow-up records of recurrence and death.

**Study Population**

All patients who underwent complete resection of colorectal liver-limited metastases with confirmed pathologic diagnosis were enrolled in this study. Seventy years of age was defined as the minimum age for elderly patients. Thus, the patients are divided into two groups – the YG (< 70 years of age) and the EG (≥ 70 years of age).

**Statistical Analysis**
Categorical variables were expressed as proportions and numerical variables were expressed as median and range. Categorical variables were compared by the chi-square or Fisher's exact tests as appropriate whereas numerical variables were compared using the Mann-Whitney U test. The linear correlation coefficient was used to assess a potential relationship between two numerical variables. To compensate for the biases between the YG and the EG in the unmatched cohort, the propensity score (PS) “nearest neighbor” matching method was used with a matching ratio of 1:2 for the EG and the YG. The caliper value was set at 0.05. The following variables were included in the PS matching model: gender, ASA score, comorbidities, primary N stage, number of liver metastases, preoperative CEA, preoperative CRS score, RAS/BRAF mutation status, preoperative chemotherapy cycles, history of major liver resection, history of hepatectomy combined with intraoperative RFA, history of repeat hepatectomy after recurrence and post-hepatectomy adjuvant chemotherapy. Response to preoperative chemotherapy was not included in the PS matching model due to too much missing data. Short-term results such as operation time, intraoperative blood loss, intraoperative and postoperative RBC transfusion, postoperative hospital stay, ICU stay and Clavien-Dindo grades of general or surgical complications were compared between the EG and the YG before and after PS matching. Recurrence and survival data were followed up by telephone or outpatient visit every six months following hepatectomy. Disease-free survival (DFS) was defined as the duration from the date of hepatectomy to the date of event (tumor recurrence or death) or the last follow-up. Overall survival (OS) was defined as the duration from the date of hepatectomy to the date of death or the last follow-up. Cancer-specific-survival (CSS) was defined as the duration from the date of hepatectomy to the date of cancer-related death or the last follow-up. Kaplan-Meier survival analysis was used to compare the DFS, OS and CSS before and after PS matching by the log rank test. The Cox multivariate proportional hazards model was used to identify independent prognostic factors of DFS, OS and CSS after PS matching. \( P < 0.05 \) was deemed significantly different. All statistical analyses were performed using the SPSS software package (version 23, SPSS Inc., Chicago, IL, USA).

Results

Comparison of elderly and younger patients before PS matching

Demographic characteristics and short-term outcomes

A total of 724 patients with colorectal liver-limited metastases were included in the study, with 73 patients in the EG and 651 patients in the YG. As shown in Table 1, the median age was 56 years old for the YG and 73 years old for the EG (\( p < 0.001 \)). There were 417 male patients (64.1%) in the YG and 51 male patients (69.6%) in the EG (\( p = 0.325 \)). There were 55 patients (8.4%) in the YG and 25 patients (34.2%) in the EG with an ASA score of III (\( p < 0.001 \)). There were 274 patients (42.1%) in the YG and 50 patients (68.5%) in the EG with associated comorbidities (\( p < 0.001 \)). With regards to specific comorbidities, there was a significantly higher percentage of patients with hypertension and ischemic heart disease in the EG than in the YG (\( p < 0.001 \) and \( p = 0.036 \), respectively). The distribution of other comorbidities was not
statistically different between the two groups (p > 0.05). Prognostic factors including primary tumor sidedness (left or right), primary T stage, primary N stage, distribution of liver metastases, maximum diameter of liver metastases, presence of synchronous or metachronous liver metastases, preoperative CRS score, RAS/BRAF mutation status, preoperative serum CEA and CA19-9 levels and history of repeat resection for recurrence were not significantly different between the two groups. However, a significantly greater proportion of patients had more than 3 liver metastases (31.3% vs. 19.2%, p = 0.032) or received more than six cycles of chemotherapy (13.2% vs 4.1%, p = 0.025) in the YG compared to the EG. In addition, a greater proportion of patients received postoperative adjuvant chemotherapy in the YG compared to the EG (67.9% versus 54.8%, p = 0.024). With regards to intraoperative information, a higher proportion of patients in the YG received combined hepatectomy and RFA compared to the EG (13.1% vs. 4.1%, p = 0.017). Other procedural features such as two-stage hepatectomy, simultaneous resection, major hepatectomy, Pringle clamping time of the hepaticoduodenal ligament, resection margin, intraoperative blood loss, intraoperative RBC transfusion and operation time were not significantly different between groups (p > 0.05). Regarding postoperative outcomes, the Clavien-Dindo grades of both general and surgical complications did not significantly differ between groups, nor did in-hospital or 90-day mortality (p > 0.05). However, significantly greater proportions of patients in the EG were admitted to the ICU or readmitted to the hospital postoperatively compared to the YG (11.0% vs. 2.8%, p = 0.003 and 4.1% vs. 0.5%, p = 0.016, respectively).
| Variable                                           | Aged < 70 years (n = 651) | Aged ≥ 70 years (n = 73) | P value |
|---------------------------------------------------|---------------------------|--------------------------|---------|
| Age (years)                                       | 56(19–69)                 | 73(70–83)                | < 0.001 |
| Gender, male                                      | 417(64.1%)                | 51(69.9%)                | 0.325   |
| ASA                                               |                           | 0.001                    |
| Comorbidity                                       | 274(42.1%)                | 50(68.5%)                | < 0.001 |
| Cerebrovascular disease                           | 17(2.6%)                  | 5(6.8%)                  | 0.061   |
| Arrhythmia                                        | 9(1.4%)                   | 1(1.4%)                  | 1.000   |
| Ischemic heart disease                            | 36(5.5%)                  | 9(12.3%)                 | 0.036   |
| Diabetes Mellitus                                 | 94(14.4%)                 | 15(20.5%)                | 0.166   |
| Hypertension                                      | 178(27.3%)                | 40(54.8%)                | < 0.001 |
| Chronic obstructive pulmonary disease             | 5(0.8%)                   | 2(2.7%)                  | 0.151   |
| Chronic renal dysfunction                         | 4(0.6%)                   | 1(1.4%)                  | 0.413   |
| Accompanying liver disease                        | 29(4.5%)                  | 2(2.7%)                  | 0.760   |
| Primary tumor sidedness                           |                           |                          | 0.198   |
| Right side                                        | 112(17.2%)                | 17(23.3%)                |         |
| Left side                                         | 539(82.8%)                | 56(76.7%)                |         |
| Primary T                                         |                           |                          | 0.659   |
| pT0-T2                                            | 64(9.8%)                  | 6(8.2%)                  |         |
| pT3-T4                                            | 587(90.2%)                | 67(91.8%)                |         |
| Primary N                                         |                           |                          | 0.869   |
| pN0                                               | 199(30.6%)                | 23(31.5%)                |         |
| pN1-2                                             | 452(69.4%)                | 50(68.5%)                |         |
| Number of liver metastases (LM)                   |                           |                          | 0.032   |
| Variable                                      | Aged < 70 years (n = 651) | Aged ≥ 70 years (n = 73) | P value |
|----------------------------------------------|---------------------------|--------------------------|---------|
| ≤3                                           | 447(68.7%)                | 59(80.8%)                |         |
| >3                                           | 204(31.3%)                | 14(19.2%)                |         |
| Distribution of LM                           |                           |                          | 0.084   |
| Unilobar                                     | 341(52.4%)                | 46(63.0%)                |         |
| Bilobar                                      | 310(47.6%)                | 27(37.0%)                |         |
| Maximum diameter of LM                       |                           |                          | 0.631   |
| ≤5 cm                                        | 566(86.9%)                | 62(84.9%)                |         |
| >5 cm                                        | 85(13.1%)                 | 11(15.1%)                |         |
| Temporal relationship                        |                           |                          | 0.796   |
| Synchronous                                  | 367(56.4%)                | 40(54.8%)                |         |
| Metachronous                                 | 284(44.6%)                | 33(45.2%)                |         |
| Preoperative chemotherapy cycles             |                           |                          | 0.025   |
| ≤6cycles                                     | 565(86.8%)                | 70(95.9%)                |         |
| >6 cycles                                    | 86(13.2%)                 | 3(4.1%)                  |         |
| Preoperative clinical risk score (CRS)       |                           |                          | 0.590   |
| 0–2                                          | 344(52.8%)                | 41(56.2%)                |         |
| 3–5                                          | 307(47.2%)                | 32(43.8%)                |         |
| RAS/BRAF mutation                            | 215(33.0%)                | 27(37.0%)                | 0.496   |
| Preoperative CEA (ng/ml)                     | 8.19(0.47–1351.00)        | 8.53(1.23–224.80)        | 0.566   |
| Preoperative CA19-9 (U/ml)                   | 22.03(0.00-29909.00)      | 24.56(0.00-1354.00)      | 0.633   |
| Repeat resection after recurrence            | 73(11.2%)                 | 8(11.0%)                 | 0.948   |
| Postoperative chemotherapy                   | 442(67.9%)                | 40(54.8%)                | 0.024   |
| Combination with RFA                         | 85(13.1%)                 | 3(4.1%)                  | 0.027   |
| Two stage hepatectomy                        | 9(1.4%)                   | 1(1.4%)                  | 1.000   |
| Simultaneous resection                       | 120(18.4%)                | 17(23.3%)                | 0.315   |
| Major hepatectomy                            | 127(19.5%)                | 9(12.3%)                 | 1.136   |
| Pringle clamp                                | 513(78.8%)                | 53(72.6%)                | 0.224   |
| Variable                                      | Aged < 70 years (n = 651) | Aged ≥ 70 years (n = 73) | P value |
|----------------------------------------------|---------------------------|--------------------------|---------|
| Pringle clamping time (min)                  | 20(0–98)                  | 15(0–60)                 | 0.061   |
| R1 margin                                    | 96(14.7%)                 | 7(9.6%)                  | 0.232   |
| Intraoperative blood loss (ml)               | 200(0–6500)               | 150(20–1000)             | 0.529   |
| Intraoperative RBC transfusion               | 28(4.3%)                  | 5(6.8%)                  | 0.367   |
| Intraoperative RBC transfused (U)            | 4(1–12)                   | 3(2–4)                   | 0.269   |
| Operation time (min)                         | 187(32–600)               | 180(60–330)              | 0.146   |
| Hospital stay (days)                         | 9(4–78)                   | 9(4–48)                  | 0.909   |
| Postoperative complications                  | 186(28.6%)                | 20(27.4%)                | 0.833   |
| Clavien-Dindo classification                 |                           |                          | 0.262   |
| [I]                                          | 106(57.0%)                | 14(70.0%)                |         |
| [II]                                         | 80(43.0%)                 | 6(30.0%)                 |         |
| General complications                        | 58(8.9%)                  | 4(5.5%)                  | 0.321   |
| Postoperative heart failure                  | 2(0.3%)                   | 0(0%)                    | 1.000   |
| Postoperative coronary artery disease        | 6(0.9%)                   | 0(0%)                    | 1.000   |
| Postoperative arrhythmia                     | 8(1.2%)                   | 1(1.4%)                  | 1.000   |
| Postoperative lung infection                 | 5(0.8%)                   | 1(1.4%)                  | 0.473   |
| Postoperative renal failure                  | 2(0.3%)                   | 0(0%)                    | 1.000   |
| Postoperative pulmonary embolism            | 1(0.2%)                   | 0(0%)                    | 1.000   |
| Postoperative deep vein thrombosis           | 2(0.3%)                   | 0(0%)                    | 1.000   |
| Postoperative urinary infection              | 4(0.6%)                   | 0(0%)                    | 1.000   |
| Postoperative pleural effusion              | 28(4.3%)                  | 2(2.7%)                  | 0.759   |
| Postoperative stress ulcer                   | 6(0.9%)                   | 1(1.4%)                  | 0.526   |
| Surgical complications                       | 129(19.8%)                | 11(15.1%)                | 0.330   |
| Posthepatectomy liver failure                | 22(3.4%)                  | 2(2.7%)                  | 1.000   |
| Postoperative abdominal infection            | 53(8.1%)                  | 7(9.6%)                  | 0.671   |
| Postoperative bile leakage                   | 37(5.7%)                  | 3(4.1%)                  | 0.788   |
| Postoperative abdominal collection           | 22(3.4%)                  | 2(2.7%)                  | 1.000   |
| Variable                                         | Aged < 70 years (n = 651) | Aged ≥ 70 years (n = 73) | P value |
|-------------------------------------------------|--------------------------|--------------------------|---------|
| Incision infection                              | 9(1.4%)                  | 0(0%)                    | 0.610   |
| Postoperative ileus                             | 12(1.8%)                 | 0(0%)                    | 0.622   |
| Postoperative abdominal bleeding                 | 26(4.0%)                 | 1(1.4%)                  | 0.508   |
| ICU                                             | 18(2.8%)                 | 8(11.0%)                 | 0.003   |
| ICU stay (days)                                 | 1(1–6)                   | 1.5(1–6)                 | 0.927   |
| Postoperative RBC transfusion                   | 50(7.7%)                 | 7(9.6%)                  | 0.566   |
| Postoperative RBC transfused (U)                | 4(2–58)                  | 2(2–6)                   | 0.510   |
| Reoperation                                      | 12(1.8%)                 | 0(0%)                    | 0.622   |
| Readmission                                     | 3(0.5%)                  | 3(4.1%)                  | 0.016   |
| Mortality (in-hospital)                         | 1(0.2%)                  | 0(0%)                    | 1.000   |
| Mortality (90-day)                              | 1(0.2%)                  | 0(0%)                    | 1.000   |
| Recurrence                                      | 467(71.7%)               | 49(67.1%)                | 0.409   |
| Intrahepatic recurrence                        | 355(54.5%)               | 40(54.8%)                | 0.966   |
| Extrahepatic recurrence                        | 112(17.2%)               | 9(12.3%)                 | 0.290   |
| Disease-free survival                           |                          |                          | 0.374   |
| 1-year                                          | 46.6%                    | 50.5%                    |         |
| 3-year                                          | 26.2%                    | 31.0%                    |         |
| 5-year                                          | 23.5%                    | 25.5%                    |         |
| Overall survival                                |                          |                          | 0.219   |
| 1-year                                          | 94.1%                    | 90.4%                    |         |
| 3-year                                          | 60.5%                    | 56.3%                    |         |
| 5-year                                          | 48.7%                    | 43.6%                    |         |
| Cancer specific survival                        |                          |                          | 0.512   |
| 1-year                                          | 94.4%                    | 90.4%                    |         |
| 3-year                                          | 61.1%                    | 59.0%                    |         |
| 5-year                                          | 49.2%                    | 45.7%                    |         |

Long-term outcomes
The median follow-up period was 28.4 months. The recurrence rates – including both intrahepatic and extrahepatic recurrence – were not significantly different between the EG and YG (p > 0.05). There was also no significant difference in 1-year, 3-year or 5-year DFS, OS or CSS survival rates (p > 0.05; Table 1 and Fig. 1A-C).

Comparison of elderly and younger patients after PS matching

Demographic characteristics and short-term outcomes

After PS matching for preoperative and prognostic factors that differed significantly between groups, a total of 64 cases from the EG and 128 cases from the YG were considered for matched analysis. As shown in Table 2, the median ages of the EG and YG groups were 72.5 and 57 years old, respectively (p < 0.001). When the biases associated with differences in ASA score, comorbidities, number of liver metastases, number of preoperative chemotherapy cycles, intraoperative RFA and postoperative adjuvant chemotherapy were removed by PS matching, the following intraoperative and postoperative differences between the groups were found. First, the median intraoperative blood loss in the YG was significantly higher than that in the EG (200 mL vs 175 mL, p = 0.046), and the median postoperative hospital stay was significantly longer in the YG than the EG (11 days vs. 8 days, p = 0.020). However, the readmission rate of the EG was still significantly greater than that of YG (4.7% vs. 0.0%, p = 0.036). Other postoperative variables, such as Clavien-Dindo grades for surgical and general complications, postoperative ICU stay, postoperative RBC transfusion and reoperation rate, were not significantly different between groups (p > 0.05). In addition, the in-hospital and 90-day mortality rates were similar between the two groups (p > 0.05).
Table 2
Demographics comparison of the elderly and younger patients after PS matching

| Variable                                | Aged < 70 years (n = 128) | Aged ≥ 70 years (n = 64) | P value |
|-----------------------------------------|---------------------------|--------------------------|---------|
| Age (years)                             | 57(31–69)                 | 72.5(70–83)              | < 0.001 |
| Gender, male                            | 73(57.0%)                 | 43(67.2%)                | 0.175   |
| ASA                                     |                           |                          | 0.200   |
| Comorbidity                             | 65(50.8%)                 | 41(61.1%)                | 0.081   |
| Cerebrovascular disease                 | 4(3.1%)                   | 2(3.1%)                  | 1.000   |
| Arrhythmia                              | 3(2.3%)                   | 1(1.6%)                  | 1.000   |
| Ischemic heart disease                  | 11(8.6%)                  | 6(9.4%)                  | 0.857   |
| Diabetes Mellitus                       | 21(16.4%)                 | 12(18.8%)                | 0.685   |
| Hypertension                            | 49(38.3%)                 | 31(48.4%)                | 0.178   |
| Chronic obstructive pulmonary disease   | 0(0.0%)                   | 1(1.6%)                  | 0.333   |
| Chronic renal dysfunction               | 0(0.0%)                   | 1(1.6%)                  | 0.333   |
| Accompanying liver disease              | 10(7.8%)                  | 2(3.1%)                  | 0.343   |
| Primary tumor sidedness                 |                           |                          | 0.447   |
| Right side                              | 24(18.8%)                 | 15(23.4%)                |         |
| Left side                               | 104(81.3%)                | 49(76.6%)                |         |
| Primary T                               |                           |                          | 0.557   |
| pT0-T2                                  | 8(6.3%)                   | 6(9.4%)                  |         |
| pT3-T4                                  | 120(93.8%)                | 58(90.6%)                |         |
| Primary N                               |                           |                          | 0.653   |
| pN0                                     | 36(28.1%)                 | 20(31.3%)                |         |
| pN1-2                                   | 92(71.9%)                 | 44(68.8%)                |         |
| Number of liver metastases (LM)         |                           |                          | 0.433   |
| ≤ 3                                     | 106(82.8%)                | 50(78.1%)                |         |
| Variable                                      | Aged < 70 years (n = 128) | Aged ≥ 70 years (n = 64) | P value |
|----------------------------------------------|---------------------------|--------------------------|---------|
| >3                                           | 22(17.2%)                 | 14(21.9%)                | 1.000   |
| Distribution of LM                           |                           |                          | 1.000   |
| Unilobar                                     | 80(62.5%)                 | 40(62.5%)                |         |
| Bilobar                                      | 48(37.5%)                 | 24(37.5%)                |         |
| Maximum diameter of LM                       |                           |                          | 0.509   |
| ≤ 5 cm                                       | 103(80.5%)                | 54(84.4%)                |         |
| >5 cm                                        | 25(19.5%)                 | 10(15.6%)                |         |
| Temporal relationship                        |                           |                          | 0.126   |
| Synchronous                                  | 61(47.7%)                 | 38(59.4%)                |         |
| Metachronous                                 | 67(52.3%)                 | 26(40.6%)                |         |
| Preoperative chemotherapy cycles              |                           |                          | 1.000   |
| ≤ 6 cycles                                   | 122(95.3%)                | 61(95.3%)                |         |
| >6 cycles                                    | 6(4.7%)                   | 3(4.7%)                  |         |
| Preoperative clinical risk score (CRS)       |                           |                          | 0.535   |
| 0–2                                          | 76(59.4%)                 | 35(54.7%)                |         |
| 3–5                                          | 52(40.6%)                 | 29(45.3%)                |         |
| RAS/BRAF mutation                            | 47(36.9%)                 | 22(34.4%)                | 0.750   |
| Preoperative CEA (ng/ml)                     | 9.10(0.93–794.50)         | 9.41(1.23–224.80)        | 0.858   |
| Preoperative CA19-9 (U/ml)                   | 28.11(0.00–28385.00)      | 24.06(0.00–1354.00)      | 0.360   |
| Repeat resection after recurrence            | 20(15.6%)                 | 8(12.5%)                 | 0.563   |
| Postoperative chemotherapy                   | 86(67.2%)                 | 38(59.4%)                | 0.286   |
| Combination with RFA                         | 1(0.8%)                   | 3(4.7%)                  | 0.109   |
| Two stage hepatectomy                        | 1(0.8%)                   | 1(1.6%)                  | 1.000   |
| Simultaneous resection                       | 17(13.3%)                 | 16(25.0%)                | 0.066   |
| Major hepatectomy                            | 24(18.8%)                 | 8(12.5%)                 | 0.273   |
| Pringle clamp                                | 95(74.2%)                 | 44(68.8%)                | 0.424   |
| Pringle clamping time (min)                  | 15(0–60)                  | 15(0–60)                 | 0.465   |
| Variable                              | Aged < 70 years (n = 128) | Aged ≥ 70 years (n = 64) | P value |
|--------------------------------------|---------------------------|--------------------------|---------|
| R1 margin                            | 3(2.3%)                   | 6(9.4%)                  | 0.062   |
| Intraoperative blood loss (ml)       | 200(20-6500)              | 175(20–800)              | 0.046   |
| Intraoperative RBC transfusion       | 10(7.9%)                  | 3(4.7%)                  | 0.549   |
| Intraoperative RBC transfused (U)    | 0(0–8)                    | 0(0–4)                   | 0.313   |
| Operation time (min)                 | 172.5(60–570)             | 180(60–327)              | 0.799   |
| Postoperative hospital stay (days)   | 11(4–70)                  | 8(4–48)                  | 0.020   |
| Postoperative complications          | 37(28.9%)                 | 17(26.6%)                | 0.733   |
| Clavien-Dindo classification         |                           |                          | 0.062   |
| I-II                                 | 16(43.2%)                 | 12(70.6%)                |         |
| I-III                                | 21(56.8%)                 | 5(29.4%)                 |         |
| General complications                | 15(11.7%)                 | 4(6.3%)                  | 0.232   |
| Postoperative heart failure          | 0(0.0%)                   | 0(0%)                    | -       |
| Postoperative coronary artery disease| 2(1.6%)                   | 0(0%)                    | 0.553   |
| Postoperative arrhythmia             | 0(0.0%)                   | 1(1.6%)                  | 0.333   |
| Postoperative lung infection         | 1(0.8%)                   | 1(1.6%)                  | 1.000   |
| Postoperative renal failure          | 0(0.0%)                   | 0(0.0%)                  | -       |
| Postoperative pulmonary embolism     | 1(0.8%)                   | 0(0.0%)                  | 1.000   |
| Postoperative deep vein thrombosis   | 0(0.0%)                   | 0(0.0%)                  | -       |
| Postoperative urinary infection      | 0(0.0%)                   | 0(0.0%)                  | -       |
| Postoperative pleural effusion       | 10(7.8%)                  | 2(3.1%)                  | 0.343   |
| Postoperative stress ulcer           | 1(0.8%)                   | 1(1.6%)                  | 1.000   |
| Surgical complications               | 24(18.8%)                 | 8(12.5%)                 | 0.273   |
| Posthepatectomy liver failure        | 2(1.6%)                   | 1(1.6%)                  | 1.000   |
| Postoperative abdominal infection     | 3(2.3%)                   | 5(7.8%)                  | 0.120   |
| Postoperative bile leakage           | 8(6.3%)                   | 2(3.1%)                  | 0.500   |
| Postoperative abdominal collection   | 4(3.1%)                   | 2(3.1%)                  | 1.000   |
| Incision infection                   | 3(2.3%)                   | 0(0.0%)                  | 0.552   |
| Variable                                | Aged < 70 years (n = 128) | Aged ≥ 70 years (n = 64) | \( P \) value |
|-----------------------------------------|---------------------------|--------------------------|--------------|
| Postoperative ileus                     | 4 (3.1%)                  | 0 (0.0%)                 | 0.303        |
| Postoperative abdominal bleeding        | 5 (3.9%)                  | 1 (1.6%)                 | 0.666        |
| ICU                                     | 5 (3.9%)                  | 6 (9.4%)                 | 0.185        |
| ICU stay (days)                         | 2 (1–6)                   | 1.5 (1–6)                | 0.537        |
| Postoperative RBC transfusion           | 11 (8.6%)                 | 7 (10.9%)                | 0.599        |
| Postoperative RBC transfused (U)        | 4 (2–58)                  | 2 (2–6)                  | 0.151        |
| Reoperation                             | 4 (3.1%)                  | 0 (0.0%)                 | 0.303        |
| Readmission                             | 0 (0.0%)                  | 3 (4.7%)                 | 0.036        |
| Mortality (in-hospital)                 | 1 (0.8%)                  | 0 (0.0%)                 | 1.000        |
| Mortality (90-day)                      | 1 (0.8%)                  | 0 (0.0%)                 | 1.000        |
| Recurrence                              | 102 (79.7%)               | 43 (67.2%)               | 0.058        |
| Intrahepatic recurrence                 | 70 (54.7%)                | 34 (53.1%)               | 0.838        |
| Extrahepatic recurrence                 | 32 (25.0%)                | 9 (14.1%)                | 0.081        |
| Disease-free survival                   |                           |                          | 0.269        |
| 1-year                                  | 43.5%                     | 51.4%                    |              |
| 3-year                                  | 21.2%                     | 30.3%                    |              |
| 5-year                                  | 18.5%                     | 24.1%                    |              |
| Overall survival                        |                           |                          | 0.401        |
| 1-year                                  | 89.0%                     | 89.1%                    |              |
| 3-year                                  | 47.8%                     | 57.7%                    |              |
| 5-year                                  | 32.7%                     | 45.4%                    |              |
| Cancer specific survival                |                           |                          | 0.163        |
| 1-year                                  | 89.8%                     | 89.1%                    |              |
| 3-year                                  | 48.2%                     | 61.1%                    |              |
| 5-year                                  | 32.9%                     | 48.0%                    |              |

**Long-term outcomes**
The median follow-up period for the matched patient groups was 29.8 months. The recurrence rates – including both intra- and extra-hepatic recurrence – between the EG and YG were not significantly different (p > 0.05). The 1-year, 3-year and 5-year DFS, OS and CSS survival rates were higher in the EG than in the YG; however this difference was not statistically significant (p > 0.05; Table 2 and Fig. 1D-F). In the EG, the 5-year DFS, OS and CSS rates were 24.1%, 45.4% and 48.0%, respectively; the median lengths of DFS, OS and CSS were 12.3 months, 45.3 months and 58.2 months respectively. In the YG, the 5-year DFS, OS and CSS rates were 18.5%, 32.7% and 32.9% respectively; the median lengths of DFS, OS and CSS were 10.2 months, 33.5 months and 33.5 months respectively.

**Cox proportional hazards model analysis**

Cox multivariate regression analysis was performed for the PS matched cohort, which included 64 EG patients and 128 YG patients. As shown in Table 3, RAS/BRAF mutation status, preoperative serum CEA levels ≥ 20 ng/mL, preoperative CRS ≥ 3, and the presence of > 3 liver metastases were identified as independent predictive factors of DFS (p < 0.05). Preoperative serum CEA levels ≥ 20 ng/mL and preoperative CRS ≥ 3 were identified as independent predictive factors of both OS and CSS (p < 0.05). Notably, old age (≥ 70 years) was not identified as an independent predictive factor for DFS, OS or CSS (p > 0.05).
Table 3
Multivariate Cox Regression analyses of disease-free survival, overall survival and cancer specific survival after PS matching

| Variable                                  | Relative ratio | 95% Confidence interval | P value |
|-------------------------------------------|----------------|-------------------------|---------|
| Disease-free survival                     |                |                         |         |
| Age (≥ 70 years old)                      | 0.860          | 0.602–1.230             | 0.409   |
| RAS/BRAF mutation                         | 1.558          | 1.117–2.174             | 0.009   |
| Preoperative CEA (≥ 20 ng/ml)             | 1.635          | 1.155–2.314             | 0.006   |
| Preoperative CRS (≥ 3)                     | 1.637          | 1.142–2.347             | 0.007   |
| Number of Liver metastases (> 3)          | 1.732          | 1.120–2.678             | 0.014   |
| Overall survival                           |                |                         |         |
| Age (≥ 70 years old)                      | 0.828          | 0.550–1.247             | 0.367   |
| RAS/BRAF mutation                         | 1.432          | 0.985–2.081             | 0.060   |
| Preoperative CEA (≥ 20 ng/ml)             | 1.699          | 1.157–2.497             | 0.007   |
| Preoperative CRS (≥ 3)                     | 1.638          | 1.141–2.352             | 0.007   |
| Cancer specific survival                   |                |                         |         |
| Age (≥ 70 years old)                      | 0.699          | 0.455–1.076             | 0.103   |
| RAS/BRAF mutation                         | 1.348          | 0.911–1.994             | 0.136   |
| Preoperative CEA (≥ 20 ng/ml)             | 2.008          | 1.358–2.968             | <0.001  |
| Preoperative CRS (≥ 3)                     | 1.548          | 1.069–2.241             | 0.021   |

Discussion

With the increasing age of the global population, stage IV colorectal cancer is being diagnosed in elderly patients more frequently than ever before [10]. As a result of extensive progress in surgical and anesthetic techniques and modern chemotherapy regimens, more patients can undergo resection of liver metastases with curative intent. This has been proven to be the most effective treatment strategy for colorectal liver metastases (CRLM). However, the increasing possibility of age-related comorbidities and high ASA scores among the elderly patients undergoing hepatectomy poses a higher risk of postoperative morbidity and mortality. Although some previous literature reported that older patients had similar surgical safety and long-term survival compared with younger patients, baseline data for both groups were not balanced. Some important prognostic factors such as RAS/BRAF mutation and primary tumor sidedness were also not included in published studies. Therefore, this study, which compared the short-term and long-term
results of hepatectomy for younger and elderly patients, was designed to overcome the above-mentioned drawbacks.

There are different definitions in the literature as to the cutoff age for an individual to be designated as elderly [11, 17, 18, 20]. However, the most frequently used cutoff age is 70 [21], which was adopted for the EG cutoff in this study. Due to the unmatched demographic and preoperative treatment data between the EG and the YG in this study, a PSM method was used to probe the effect of age on patient outcomes after hepatectomy. Vito De Blasi et al. [20] also used this method to mitigate potential biases between groups. However, despite the PSM approach, there were still some unmatched parameters between the groups – namely pedicle clamping duration and recurrence treatment protocol – which resulted in some inconclusive analyses. Furthermore, most previous studies have enrolled patients with EHD, which makes accurate definition of DFS challenging. To overcome this disadvantage, we excluded all patients with EHD from analysis in this study.

Before propensity score matching, there were biases in the baseline data between the EG and the YG due to differences in comorbidities and ASA scores. In addition, some perioperative factors – such as the proportion of patients who had > 3 liver metastases, received more than six cycles of preoperative chemotherapy, received postoperative chemotherapy or underwent intraoperative RFA – were also significantly different between the YG and EG. Importantly, it has been reported that more than six cycles of preoperative chemotherapy and intraoperative RFA may increase postoperative morbidity; furthermore, having > 3 liver metastases and receiving postoperative adjuvant chemotherapy are important prognostic factors for patients with CRLM [22, 23]. Propensity score matching was used to balance the distribution of these variables between groups in this study. After matching, short-term patient outcomes revealed that the EG had significantly less intraoperative blood loss and a shorter postoperative hospital stay – though a higher readmission rate – compared to the YG. Long-term outcomes demonstrate a slight, but non-statistically significant improvement, in 5-year DFS, OS and CSS for the EG compared with the YG.

For modern treatment of CRLM, routine testing of RAS/BRAF mutation status has been recommended since 2014 as it has been confirmed to be a negative prognostic factor for CRLM patients [24]. It has been reported that positive RAS/BRAF mutation status is associated with shorter DFS and OS and narrower margin widths after hepatectomy compared to wild type RAS/BRAF [25–27]. However, RAS/BRAF mutation status has never been considered in previous retrospective studies, as much of the data precedes standard testing for RAS/BRAF status. In this study, all tumor tissue samples from the considered patients were retrieved from the pathology department and tested for RAS/BRAF mutation status, which was matched between the two groups after PSM.

Primary tumor sidedness has also been emphasized in recent years in recognition of the fact that the side of origin plays a role in tumor behavior and progression. It was reported that tumors originating on the right were more frequently associated with female patients, the elderly, high grade (poor differentiation), BRAF mutations, the enhanced CpG island methylator phenotype, high microsatellite instability and high expression of consensus molecular subtypes 1 and 3 compared with left-side origin tumors [28]. These
characteristics negatively affect anti-EGFR treatment and the prognosis of patients with right-sided tumors [29]. Therefore, we included primary tumor sidedness in our PSM model to balance the possible bias associated with this disease feature.

The CRS was proposed in 1999 by Fong et al. [30] as a prognostic indicator composed of five preoperative variables: preoperative CEA > 200 ng/mL, primary positive lymph nodes, an interval of < 12 months between diagnosis of the primary tumor and liver metastasis, presence of multiple liver metastases and maximal diameter of liver metastases > 5 cm. It has been shown that increased CRS is associated with an increased risk of postoperative recurrence and death [31]. Thus, it was important to include CRS in our PSM analysis to appropriately examine the effect of age on survival.

This study revealed no significant difference in either general or surgical postoperative complications between the EG and the YG. This result aligns with previous studies and suggests that surgery for elderly patients is as safe as it would be for younger patients with the same ASA score and comorbidities [20, 32]. This holds even when simultaneous resection of primary and liver tumors or major hepatectomy is performed. Interestingly, compared to the YG, the EG was found to have significantly less intraoperative blood loss (175 mL vs. 200 mL, p = 0.046) and a shorter median postoperative hospital stay (8 days vs. 11 days, p = 0.020), which might reflect that appropriately selected elderly recover promptly from surgery. However, the EG group did have a significantly higher readmission rate than the YG (4.7% vs. 0%, p = 0.036). Although the median intraoperative blood loss of the YG is higher than that of the EG, an absolute difference of 25 mL is of little clinical significance. The significance of the difference between groups may result from the relatively small sample size of this study, considering the p value approaching 0.05. With a larger sample size and improved matching between the groups with regards to perioperative details – such as preoperative chemotherapy, major hepatectomy, simultaneous resection and Pringle clamping time – the intraoperative blood loss will likely be comparable between the EG and the YG.

The three patients from the EG who were readmitted to the hospital were all 71 years of age. The first patient was diagnosed with synchronous descending colon cancer with liver metastases; he had concomitant hypertension but no history of diabetes. The patient received simultaneous resection of the primary tumor and liver metastases. Postoperative recovery was uneventful, and the patient was discharged after 2 weeks. However, the patient was readmitted due to incisional infection two months after discharge. The infected wound was opened and treated at the bedside, and the patient was re-discharged 3 days later. Wound infection is a Clavien-Dindo Grade I complication, but it was unusual that an incisional infection arose 2 months postoperatively. We believe that this may have resulted from the high infection risk of synchronous resection and postoperative adjuvant chemotherapy, which may have weakened the patient's immunity. The second readmitted patient was diagnosed with bilobar liver metastases after resection of sigmoid colon cancer, with concomitant coronary artery disease. He received liver resection for the bilobar metastases and was discharged 2 weeks after the operation. However, he was readmitted to the hospital one month later due to a fever of 38.3°C. Laboratory tests showed a normal white blood cell count, and radiological examinations revealed no signs of abdominal or thoracic collection. He was re-discharged 4 days later with a normal temperature and we deemed that
this complication was likely not related to the surgery. The third readmitted patient was diagnosed with multiple liver metastases after resection of ascending colon cancer, with concomitant hypertension and coronary heart disease. He received hepatectomy and intraoperative RFA for multiple tumors and postoperative abdominal infection occurred. He was discharged 46 days after the operation after undergoing percutaneous puncture and abdominal drainage for the infection. However, he was readmitted to the hospital 10 days later due to fever of 38.5℃. The white blood cell count was marginally elevated, and ultrasound showed a small thoracic collection without abdominal fluid. After treatment with antibiotics, he was re-discharged 5 days later, though it cannot be definitively determined whether this was a postoperative complication. In brief, although three patients from the EG were readmitted to the hospital, only one of them experienced an unequivocal surgical complication (incisional infection), which classified as a minor complication. None of the readmitted patients experienced systemic complications related to old age. When the length of hospital stay after readmission was added to the length of the postoperative hospital stay, the median total length of postoperative hospital stay was still significantly longer in the YG than in the EG (11 days vs. 8 days,p = 0.024). As such, we do not believe that the EG’s length of stay advantage compared to the YG was offset by the higher readmission rate.

With regards to the median length of postoperative stay being shorter in EG patients compared to YG patients, we found that the proportions of major hepatectomy and grade III or higher postoperative complications were much higher in the YG than the EG (18.8% vs. 12.5% and 56.8% vs. 29.4%, respectively), although this was not statistically significant. Given the relatively small sample size of our study, the significantly shorter postoperative length of stay in the EG may result from these differences. Thus, this result should be clarified in larger studies in the future. Regarding long-term patient outcomes, surprisingly, the 5-year DFS, OS and CSS rates were increased by 5.6%, 12.7% and 15.1%, respectively, for the EG compared to the YG, although these differences were not statistically significant. Importantly, it was shown that the OS and CSS of the YG were longer than those of the EG prior to PSM. This discrepancy may arise due to the following factors. First, some research [33, 34] has shown that the malignancy of tumors in the elderly population may be reduced; thus, the potential for tumor growth and metastasis may be decreased in the elderly as well. Second, some factors such as RAS/BRAF mutation status, primary tumor sidedness and history of preoperative chemotherapy were included in our study and balanced between the EG and YG by PSM. These important prognostic factors were lacking in previously published studies, which may contribute to the difference in OS identified in our study. Notably, due to the relatively small sample size of this study, this conclusion should be confirmed by high-quality studies with a larger sample size in the future.

This study has some limitations. First, similar to other studies, this study had a relatively small sample size. After eliminating patients with EHD and unmatched patients, there were only 64 patients in the EG and 128 patients in the matched YG considered for analysis, which may impact the representativeness and robustness of the results. As such, the results of this study should be confirmed by high-quality studies with larger sample sizes in the future. Another limitation is the retrospective nature of this study; so the conclusion should be evaluated by large prospective controlled trials in future work. Finally, the third limitation is the loss of information regarding the response to preoperative chemotherapy, which has
been shown in previous work to be a pivotal prognostic factor for CRLM patients undergoing hepatectomy [31, 35].

**Conclusions**

For appropriately identified elderly patients with colorectal liver-limited metastases, hepatectomy is safe and effective. In this study, we found that there was no increase in postoperative morbidities and mortality compared with matched younger patients. Importantly, elderly patients may benefit from longer DFS, OS and CSS after hepatectomy; thus, this procedure should be performed for elderly patients who are fit for surgery.

**Abbreviations**

PSM: propensity score matching; YG: younger group; EG: elderly group; OS: overall survival; DFS: disease-free survival; CSS: cancer-specific survival; RAS: rat sarcoma virus proto-oncogene; BRAF: B-Raf proto-oncogene; EHD: extrahepatic diseases; ASA: American Society of Anesthesiologists; CRS: clinical risk score; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; RBC: red blood cell; RFA: radiofrequency ablation; CRLM: colorectal liver metastases.

**Declarations**

**Ethics approval and consent to participate**

The Ethics Committee of Beijing Cancer Hospital approved the study protocol, which was performed in compliance with the Helsinki Declaration.

**Consent for publication**

We just extracted data and did not involve the private information of patients.

**Availability of data and materials**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Competing interests**

There are no conflicts of interest to declare.
Funding

This work was supported by the National Natural Science Foundation of China (grant No. 81874143 and No. 31971192) and the Natural Science Foundation of Beijing Municipality (grant No. 7192035).

Authors' contributions

KM J designed the study, analyzed the data, and wrote the manuscript. K W, Q B and HW W participated the data collection. BC X participated in the study design and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Mr. Wen-Wu He and Miss Cathy He for their efforts in revising the manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Leporrier J, Maurel J, Chiche L, et al. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg. 2006;93(4):465–74.
3. van der Pool AE, Damhuis RA, Ijzermans JN, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. Colorectal Dis. 2012;14(1):56–61.
4. Morris EJ, Forman D, Thomas JD, et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg. 2010;97(7):1110–8.
5. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250(3):440–8.
6. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247(1):125–35.
7. Wei AC, Greig PD, Grant D, et al. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006;13(5):668–76.
8. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66.
9. Mavros MN, Hyder O, Pulitano C, et al. Survival of patients operated for colorectal liver metastases and concomitant extra-hepatic disease: external validation of a prognostic model. J Surg Oncol.
10. Soreide K, Wijnhoven BP. Surgery for an ageing population. Br J Surg. 2016;103(2):e7–9.
11. Adam R, Frilling A, Elias D, et al. Liver resection of colorectal metastases in elderly patients. Br J Surg. 2010;97(3):366–76.
12. Mann CD, Neal CP, Pattenden CJ, et al. Major resection of hepatic colorectal liver metastases in elderly patients - an aggressive approach is justified. Eur J Surg Oncol. 2008;34(4):428–32.
13. Bockhorn M, Sotiropoulos GC, Sgourakis G, et al. Major liver resections in the elderly-is an aggressive approach justified? Int J Colorectal Dis. 2009;24(1):83–6.
14. Kulik U, Framke T, Grosshennig A, et al. Liver resection of colorectal liver metastases in elderly patients. World J Surg. 2011;35(9):2063–72.
15. Nachmany I, Pencovich N, Zohar N, et al. Resection of colorectal liver metastases in the elderly-Is it justified? J Surg Oncol. 2016;113(5):485–8.
16. Tufo A, Dunne DF, Manu N, et al. Changing outlook for colorectal liver metastasis resection in the elderly. Eur J Surg Oncol. 2019;45(4):635–43.
17. Cook EJ, Welsh FK, Chandrakumaran K, et al. Resection of colorectal liver metastases in the elderly: does age matter? Colorectal Dis. 2012;14(10):1210–6.
18. Booth CM, Nanji S, Wei X, Mackillop WJ. Management and Outcome of Colorectal Cancer Liver Metastases in Elderly Patients: A Population-Based Study. JAMA Oncol. 2015;1(8):1111–9.
19. Kumari S, Semira C, Lee M, et al. Resection of colorectal cancer liver metastases in older patients. ANZ J Surg. 2020. doi:10.1111/ans.15750.
20. De Blasi V, Memeo R, Adam R, et al. Major Hepatectomy for Colorectal Liver Metastases in Patients Aged Over 80: A Propensity Score Matching Analysis. Dig Surg. 2018;35(4):333–41.
21. van Tuil T, Dhaif AA, Te Riele WW, et al. Systematic Review and Meta-Analysis of Liver Resection for Colorectal Metastases in Elderly Patients. Dig Surg. 2019;36(2):111–23.
22. Mima K, Beppu T, Chikamoto A, et al. Hepatic resection combined with radiofrequency ablation for initially unresectable colorectal liver metastases after effective chemotherapy is a safe procedure with a low incidence of local recurrence. Int J Clin Oncol. 2013;18(5):847–55.
23. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg. 2008;247(1):118–24.
24. Van Cutsem E, Cervantes A, Nordlinger B, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii1–9.
25. Van Cutsem E, Lenz HJ, Kohne CH, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol. 2015;33(7):692–700.
26. Brudvik KW, Mise Y, Chung MH, et al. RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases. Ann Surg Oncol. 2016;23(8):2635–43.
27. Kadowaki S, Kakuta M, Takahashi S, et al. Prognostic value of KRAS and BRAF mutations in curatively resected colorectal cancer. World J Gastroenterol. 2015;21(4):1275–83.

28. Lee MS, Menter DG, Kopetz S. Right Versus Left Colon Cancer Biology: Integrating the Consensus Molecular Subtypes. J Natl Compr Canc Netw. 2017;15(3):411–9.

29. Huemer F, Thaler J, Piringer G, et al. Sidedness and TP53 mutations impact OS in anti-EGFR but not anti-VEGF treated mCRC - an analysis of the KRAS registry of the AGMT (Arbeitsgemeinschaft Medikamentose Tumortherapie). BMC Cancer. 2018;18(1):11.

30. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18. discussion 318 – 21.

31. Xu D, Liu XF, Yan XL, et al. Survival prediction in patients with resectable colorectal liver metastases: Clinical risk scores and tumor response to chemotherapy. Oncol Lett. 2017;14(6):8051–9.

32. Nomi T, Fuks D, Kawaguchi Y, et al. Laparoscopic major hepatectomy for colorectal liver metastases in elderly patients: a single-center, case-matched study. Surg Endosc. 2015;29(6):1368–75.

33. Itzhaki O, Kaptzan T, Skutelsky E, et al. Age-adjusted antitumoral therapy based on the demonstration of increased apoptosis as a mechanism underlying the reduced malignancy of tumors in the aged. Biochim Biophys Acta. 2004;1688(2):145–59.

34. Han Z, Brown JR, Niederkorn JY. Growth and Metastasis of Intraocular Tumors in Aged Mice. Invest Ophthalmol Vis Sci. 2016;57(6):2366–76.

35. Wang K, Liu W, Yan XL, et al. Long-term postoperative survival prediction in patients with colorectal liver metastasis. Oncotarget. 2017;8(45):79927–34.

Figures

Figure 1

Comparison of disease-free survival (DFS), overall survival (OS) and cancer-specific survival (CSS) between the elderly group (EG) and the younger group (YG) before (A, B, C) and after propensity score matching (D, E, F).