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ORIGINAL ARTICLE

Simultaneous resection of colorectal cancer and synchronous liver metastases is safe for properly selected elderly patients: A retrospective study

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The present work was conducted at the Department of General Surgery, Xuanwu Hospital of Capital Medical University, Beijing, China.

Summary

Purpose: *The present study was conducted to evaluate the efficacy and safety of simultaneous resection of colorectal cancer (CRC) and synchronous liver metastases (SCRLM) in a group of elderly Chinese patients regarding the population aging in China.*

Methods: *From January 1st 2010 to May 1st 2015, 24 out of 32 elderly patients who underwent simultaneous resection of CRC and SCRLM were matched with 24 out of 55 young patients based on the propensity scores. Perioperative results and survival outcomes were compared.*

Results: *The demographic and cancer characteristics were comparable between the two groups. The postoperative duration of intensive nursing care in the elderly group was significantly longer than that in the young group [5.00 (4.00–6.75) vs. 6.50 (5.00–9.00) days, p=0.038]. No significant between-group difference was observed with respect to time to first defecation, length of postoperative hospital stay, or postoperative complication rate. There was no significant difference with respect to 3-year overall and disease-free survival rates between the two groups.*

Conclusions: *Simultaneous resection of CRC and SCRLM was safe and feasible in elderly patients, with reasonable 3-year survival rates. Age per se should not be considered as a contraindication for simultaneous resection of CRC and SCRLM.*

Key words: *colorectal cancer, elderly, liver metastases, synchronous*

Introduction

The Chinese population is aging rapidly due to the low level of fertility and mortality. It is estimated that the total number of elderly people aged ≥ 65 years in China would increase dramatically from 8.2% in 2010 to 23.9-26.9% of the total population in 2050 [1]. Among Chinese population in the age-group of 60-74 years, CRC represents the fifth most common cancer for men and the third for women; moreover, in this age-group, colorectal cancer is estimated to be the fifth leading cause of cancer-related deaths among both men and women [2]. Nearly 14-20% of CRC patients have synchronous liver metastases (SCRLM) identified during the course of diagnosis or surgery [3]. Thus, elderly patients with SCRLM are increasingly considered for surgery and/or chemotherapy.

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Currently, simultaneous resection of CRC and SCRLM has been proved safe and effective for selected patients with resectable SCRLM according to the consensus statement [3]. However, whether this simultaneous procedure is suitable for elderly patients remains to be well defined. Advanced age is associated with higher prevalence of co-morbidities and compensated systemic insufficiencies, which may increase the risks associated with major surgery [4]. However, due to advances in surgical techniques, anesthesia, critical care, and chemotherapy, major surgical procedures including colorectomy and major hepatectomy can be safely performed in some elderly patients; advanced age itself may not be considered as a surgical contraindication [5]. Thus, the present study was conducted to assess the impact of advanced age on simultaneous resection of CRC and SCRLM by analyzing the perioperative results and long-term outcomes in elderly Chinese patients.

Methods

Patient selection and eligibility

Clinical data pertaining to consecutive patients who received simultaneous resection of CRC and SCRLM at the Department of General Surgery between January 1st 2010 and May 1st 2015 were retrieved from the electronic medical records and retrospectively reviewed.

In the present study, the elderly patients (≥65 years) were matched with young patients according to the propensity scores, which were based on the following features that are putatively associated with perioperative results and longterm outcomes: the American Society of Anesthesiology (ASA) score; maximum diameter of liver metastases; number of liver metastases (<3 or ≥3); lymph node status (N2 or not); level of carcinoembryonic antigen (CEA <200 or ≥200 ng/dL); and extent of liver resection (major or minor) [6,7].

Preoperative evaluation

Preoperative complete blood and biochemical tests were routinely performed. Electrocardiogram and chest X-ray were carried out for basal cardiorespiratory evaluation. All patients had histologically proven colorectal cancer based on colonoscopic biopsy before surgery. Standard preoperative imaging included abdominopelvic computed tomography (CT) (for assessment of the primary tumor), ultrasonography and dynamic magnetic resonance imaging (MRI) of the liver (for evaluation of metastatic lesions), and chest CT scan or positron emission tomography (PET) scanning, whenever needed. All the above results and images were reviewed by a multidisciplinary team (comprising of colorectal surgeons, hepatobiliary surgeons, radiologists, oncologists, and other related specialties) to discuss the treatment strategies and to determine suitability for simultaneous resection procedure. Written informed consent was obtained from all patients and their relatives after they were informed about the details and the risks of the surgical procedure before surgery.

The eligibility criteria for simultaneous resection of CRC and SCRLM were as follows: fitness for general anesthesia, adequate volume reserve for the remnant liver function, and radical resectability of the primary as well as the metastatic lesions. The exclusion criteria were: presence of concurrent extrahepatic metastasis (e.g., peritoneal disease, nodal disease, and distant metastasis), invasion of adjacent organs, technically unresectable tumors due to vascular involvement or extensive intrahepatic lesions, and emergency surgery (e.g., CRC with perforation, obstruction, or bleeding).

For patients with unresectable SCRLM, preoperative chemotherapy was administered to achieve resectability. Intraoperative radiofrequency ablation (RFA) was employed to help reduce the extent of liver resection.

Surgical technique

All operations were performed under general anesthesia by an experienced team consisting of surgeons from both colorectal and hepatobiliary departments. The surgical principles for cancer surgery were strictly followed when performing the standard colectomy. Ultrasonic dissector (Ethicon Endo-surgery, Cincinnati, OH, USA), the ligasure vessel sealing system (Valleylab, Boulder, CO, USA), and bipolar coagulator were adopted for liver resection. Linear stapler or Hem-o-lok clips were used for division of hepatic vessels and ducts. To control bleeding during hepatectomy, pringle maneuver was performed selectively. All resections were performed with R0 intent. Intraoperative ultrasonography was applied for RFA, for detection of occult metastasis, or for assessment of the anatomical relationship between the tumor and adjacent structures. Abdominal drains were always used. Before discharge from the hospital, postoperative CT scan was performed to assess complete necrosis of liver metastasis after RFA.

Adjuvant therapy and patient follow-up

After discharge from the hospital, adjuvant chemotherapy was administered based on the patient's status, clinical performance, and the results of laboratory tests as well as imaging examinations. The follow-up period was set at 3 years. Follow-up information was collected from records of hospitalization, outpatient visits, and telephone interviews.

Definitions

Terminology for liver resections in the present study followed the Brisbane 2000 system. Major liver resection was defined as a hepatectomy involving three or more segments [3]. Postoperative complication was defined as an event occurring within 30 days after operation; severe complication was defined as Clavien-Dindo classification ≥ grade III. Death occurring within 90 days after the operation was defined as perioperative mortality.

Statistics

Categorical variables were compared using Chi-squared test or Fisher's exact test. Continuous variables

were compared using Student's *t*-test or Mann-Whitney U test, when appropriate. Cumulative overall survival (OS) rates and disease-free survival (DFS) rates were calculated using the Kaplan-Meier method and compared using the log-rank test. All tests were two-sided and $p<0.05$ was considered statistically significant. SPSS version 22.0 (SPSS, Chicago, IL, USA) was used to perform all statistical analyses.

Results

Patients and disease characteristics

Twenty-four out of the 32 elderly patients who received simultaneous resection of CRC and SCRLM were matched with 24 out of the 55 younger patients based on the closest propensity score. These matched patients constituted the elderly and young groups, respectively. The mean age of patients in the elderly and young groups was 70.00 years (range, 67.00-73.50), and 54.50 years (range, 45.25-61.00), respectively. There was no significant difference with respect to the clinical, demographic, and cancer characteristics of the two groups ($p>0.05$ for all, Table 1).

Postoperative results

There was no significant difference with respect to time to first defecation or length of hospital postoperative stay. However, the length of ICU stay in the elderly group was significantly longer than that in the young group ($p=0.038$, Table 2). The postoperative complication rate in the elderly group was comparable to that in the young group ($p=0.731$, Table 2); among them, severe complication rate (Clavien-Dindo classification ≥ grade III) in the elderly group was also comparable to that in the young group ($p=1.000$, Table 2). In the elderly group, one patient died due to rupture of spleen.

Table 1. Demographic, clinical characteristics and intraoperative results of patients in the young and elderly groups

	Young (n=24)	*Elderly (n=24)*	*p value*
Gender, n			0.233
Male	17	13	
Female	7	11	
ASA score, n			
=1	8	9	0.946
=2	10	9	
=3	6	6	
Child-Pugh score, n			0.477
A	20	18	
B	4	6	
Location of primary tumor, n			0.302
Ascending colon	9	6	
Transverse colon	1	2	
Descending colon	0	1	
Sigmoid colon	4	9	
Rectum	10	6	
Maximum diameter of primary tumor, cm	4.25 (3.50-5.50)	3.50 (2.85-4.50)	0.067
Staging of primary tumor, n			0.383
T1-T3	12	9	
T4	12	15	
Nodal status, n			0.763
N0-N1	16	15	
N2	8	9	
Location of liver metastases, n			0.505
Unilobar	17	19	
Bilobar	7	5	
Maximum diameter of liver metastases, cm	3.60 (2.70-7.78)	3.80 (2.60-5.40)	0.861
Number of liver metastases, n			0.768
<3	15	14	
≥3	9	10	

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	Young (n=24)	*Elderly (n=24)*	*p value*
Differentiation, n			0.365
Well/moderately	14	17	
Poorly/mucinous	10	7	
Carcinoembryonic antigen level (ng/dL), n			0.745
<200	17	18	
≥200	7	6	
Neoadjuvant chemotherapy, n	6	11	0.131
Operative time, min	289.04 ± 101.07	265.17 ± 85.18	0.381
Estimated blood loss, mL	200.00 (150.00-700.00)	200.00 (100.00-450.00)	0.230
Colorectal resection, n			0.302
Right colectomy	9	6	
Left colectomy	4	9	
Transverse colectomy	1	2	
Anterior rectal resection	10	6	
Abdominoperineal resection	0	1	
Liver resection, n			0.574
Sub-segmentectomy	2	0	
Segmentectomy	6	7	
Bisegmentectomy	2	4	
Sectionectomy	6	6	
Hemihepatectomy	3	1	
Atypical resection	5	6	0.731
Radiofrequency ablation, n	6	5	
Extent of liver resection, n			
Minor	16	19	0.330
Major	8	5	
Postoperative chemotherapy, n			0.160
XELOX	7	13	
FOLFOX	7	2	
FOLFIRI	5	3	
Others	5	6	

ASA: American Society of Anesthesiology. Data are presented as mean (± standard deviation), or median (range).

Table 2. Postoperative results of patients in the young and elderly groups

	Young (n=24)	*Elderly (n=24)*	*p value*
Time to first defecation, days	4.00 (3.00-5.00)	4.50 (4.00-6.00)	0.121
Length of ICU stay, days	5.00 (4.00-6.75)	6.50 (5.00-9.00)	0.038
Length of postoperative stay, days	11.50 (9.00-18.00)	11.00 (9.00-17.50)	0.836
Postoperative complications, n			
Wound infection	1	1	0.731
Rupture of incision	1	0	-
Abdominal abscess	1	1	-
Pleural effusion	1	0	-
Bile leakage	2	0	-
Intestinal fistula	0	1	-
Rupture of spleen	0	1	-
Gastrointestinal bleeding	0	1	-
Total	6	5	-
Clavien-Dindo classification ≥ III	3	4	1.000

ICU, intensive care unit. Data presented as mean (± standard deviation), or median (range)

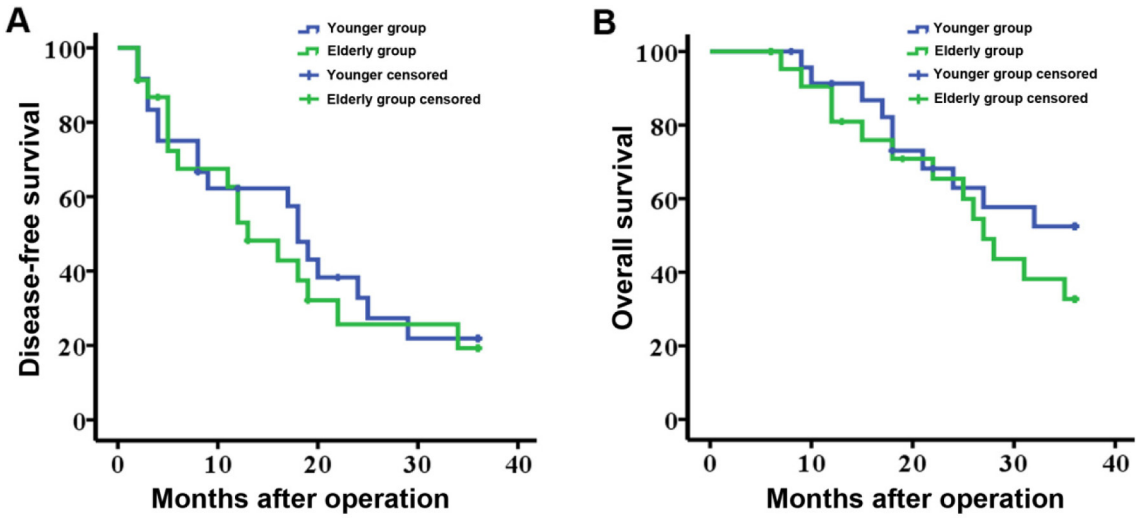

Figure 1. Disease-free survival (p=0.683) **(A)** and overall survival (p=0.288) **(B)** in elderly and young groups.

Survival outcomes

The postoperative chemotherapy regimens administered in the two groups were comparable (p=0.160; Table 1). Recurrence of liver metastatic lesions was treated with radiofrequency ablation, transcatheter arterial chemoembolization, or liver resection. The median follow-up period for patients was 26 months (range 6-85). Over a follow-up period of 36 months, four patients in the elderly group and three patients in the young group were lost to follow-up regarding DFS. For the analysis of OS, four patients in the elderly group and five patients in the young group were lost to follow-up. The 3-year DFS was 19.3% in the elderly group and 21.9% in the young group (Figure 1a). The 3-year OS was 32.7% in the elderly group and 52.4% in the young group (Figure 1b). No significant between-group differences were observed with respect to the 3-year DFS rate (p=0.683) or OS rate (p=0.288).

Discussion

In the present study the two groups were 1:1 matched, which helped minimize the effect of clinical features other than age on the perioperative results and survival outcomes. In the present study, elderly patients showed a mortality rate of 4.17% and a morbidity rate of 20.83%, which was not significantly different from that among young patients. Nagano et al [8] compared 62 elderly patients who underwent resection of colorectal metastases with 150 young patients; nearly half of the patients in both groups had received simultaneous CRC and hepatic resection. The mortality and morbidity rates for elderly patients (0% and 19.7%, respectively) were similar to those for young patients. Moreover, in the present study, the duration of intensive nursing care in the elderly group was longer than that in the young group. This indicated the importance of intensive care during postoperative management of elderly patients.

In the present study, the length of postoperative stay and time to first defecation were comparable between the two groups. This result was similar with the study conducted by Tokuhara et al [9]; they found no significant differences with respect to the length of postoperative stay or time to first defecation between elderly and young patients who had undergone laparoscopic surgery for CRC.

In a previous study, aging was shown to be associated with decreased OS rate of patients after simultaneous resection of CRC and SCRLM [10]. In the study conducted by Nagano et al [8], the 5-year OS rate of older patients was lower than that of the young patients (34.1% vs. 53.1%, respectively), while the 5-year DFS rate was comparable between the two groups. In the present study, the 3-year DFS rate was comparable between the two groups. The 3-year OS rate of elderly patients was lower than that in the young group; however, the between-group difference was not statistically significant. The relatively poor OS of elderly patients may be partly attributed to the higher incidence of non-cancer-related deaths among elderly patients during follow-up [11]. Moreover, elderly patients tend to receive less cycles of chemotherapy, and are less likely to undergo surgical treatment for hepatic recurrence owing to their poor general condition [12]. Despite the relatively lower OS rate, the comparable DFS still supports the survival benefit conferred by simultaneous resection of CRC and SCRLM for elderly patients.

Some limitations of the present study should be considered while interpreting these results.

Firstly, the small sample size and the retrospective study design are key limitations that may have introduced a possibility of selection bias. Secondly, the criterion for defining elderly patients (age ≥65 years) is different from that used in many studies. However, as a developing country, the life expectancy of Chinese population is shorter than that in developed countries. The cutoff value used in the present study may still be meaningful in the Chinese context. Thirdly, in the present study, not all patients received neoadjuvant chemotherapy, especially those with initially resectable SCRLM. Although chemo/surgery/chemo is widely applied as the standard perioperative chemotherapy, several studies suggest that patients with initially resectable CRLM should receive surgery first as neoadjuvant chemotherapy was not associated with improved overall survival [13-15]. Thus, only patients with initially unresectable SCRLM and some of those with resectable SCRLM received preoperative chemotherapy. Lastly, the role of meticulous general condition assessment and careful patient selection should not be neglected. Co-morbidities that are preoperatively assessed not only increase the difficulty in administering anesthesia and performing surgery, but are also closely related to the risk of postoperative morbidity and mortality. Thus, strict assessment and careful patient selection also contributed to the outcomes in the present study.

In summary, this propensity score analysis shows similar morbidity and mortality as well as comparable survival outcomes after simultaneous resection of CRC and CRLM between the elderly and younger patients. Although surgical decision-making is inherently challenging for elderly patients, simultaneous resection of CRC and SCRLM is safe and effective for elderly patients and age *per se*, should not be considered as an absolute contraindication.

Ethical approval

All procedures performed in studies were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of Xuanwu Hospital of Capital Medical University approved this study.

Author contribution

Yulin Guo: study conception, design, investigation, acquisition of data, interpretation draft writing.
Shun Hu: study design, investigation, analysis of data, draft writing.
Feng Cao: study conception, validation of data, interpretation, review & editing.
Dongbin Liu: study conception, interpretation, supervision, review & editing.
Fei Li: study conception, design, interpretation, supervision, review & editing, funding acquisition.

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Conflict of interests

The authors declare no conflict of interests.

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