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ORIGINAL RESEARCH

Role of Surgical Approach to Synchronous Colorectal Liver Metastases: A Retrospective Analysis

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Purpose: This study is a retrospective analysis of exploring the efficiency of surgical management on patients with synchronous colorectal liver metastasis (SCLM).

Patients and Methods: Nine hundred fifty-three consecutive patients with SCLM from Weifang People's Hospital of Shandong Province between January 2006 and December 2015 were reviewed. The values of different factors were analyzed, such as different surgical indications of liver metastases, simultaneous or staged resection of primary colorectal cancer and liver metastases, and primary tumor resection (PTR) of asymptomatic patients with unresectable liver metastases.

Results: Median survival time (47.3 months) and 5-year survival rate (31%) for patients with resected liver metastases were significantly superior to that of with nonoperative treatment (17.2 months, 4%, P<0.001); enlarging the standard of liver metastases resection can improve the resection rates (31.0% vs 13.6%, P<0.001); for patients with resectable liver metastases, the in-hospital cost for simultaneous resection group was lower than that in the staged resection group (36,698 vs 45,134 RMB, P<0.001); for patients of the asymptomatic primary tumor with unresectable liver metastases, PTR was associated with improved median survival (18.0 vs 15.0 months, P=0.006).

Conclusion: For patients with SCLM, liver resection is considered the best treatment; expanding indications of liver resection can improve the resection rates. Simultaneous resection of the primary tumor and liver metastases were indicated in patients with resectable SCLM; PTR was recommended for asymptomatic patients with unresectable hepatic metastases.

Keywords: surgical treatment, synchronous colorectal liver metastases, survival analysis, primary tumor resection

Introduction

Synchronous colorectal liver metastases (SCLM) occur in 15% to 20% of initially diagnosed colorectal patients.[1] SCLM are still the leading causes of death in colorectal patients, although the introduction of new chemotherapeutic agents and the expansion of surgical indications have improved survival in the past decades.[2] Chinese Guidelines for Diagnosis and Comprehensive Treatment of Colorectal Liver Metastases have provided new guidance for the treatment of patients with SCLM since 2010, including expanding criteria of hepatic metastases resection, simultaneous or staged resection of the primary tumor and hepatic metastases, resection of the primary tumor of asymptomatic with unresectable hepatic metastases.[3] However,

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controversy prevails amongst clinicians about which patients with SCLM are most suitable for surgical resection. The treatment process of 953 patients with SCLM was analyzed retrospectively, so as to provide experience and methods for surgical treatment.

Patients and Methods

Study Population

A total of 953 patients with SCLM treated in Weifang People's Hospital from January 2006 to December 2015 were selected. Among them, 616 (64.6%) were males and 337 (35.4%) females, with a median age of 59.7 years.

All patients were divided into two groups based on the different treatment strategies for liver metastases. A total of 252 patients (26.4%) received surgical treatment, including liver resection at the time of diagnosis (217), resection after convertible therapy (35), resection followed by adjuvant systemic chemotherapy, chemotherapy regimens were as follows: FOLFOX, FOLFIRI, XELOX with or without targeted agents. A total of 701 patients (73.6%) received non-surgical treatment, including systemic chemotherapy, hepatic artery chemotherapy, radiofrequency ablation, percutaneous ethanol injection therapy or freezing treatment of hepatic metastases (Figure 1). This study was approved by the institutional review board of Weifang People' s Hospital (the first affiliated hospital of Weifang medical college) and each patient signed an informed consent to authorize their clinical data to be used in future studies. This study was in compliance with the Declaration of Helsinki.

The indication of simultaneous resection of primary colorectal cancer and liver metastases in patients with SCLM: 1. The primary colorectal cancer could be radically resected; 2. Characteristics of hepatic metastases: 1) Remnant hepatic volume ≥30–50%, 2) Involving multiple lobes: no restriction, 3) Number of hepatic metastases: no restriction, 4)

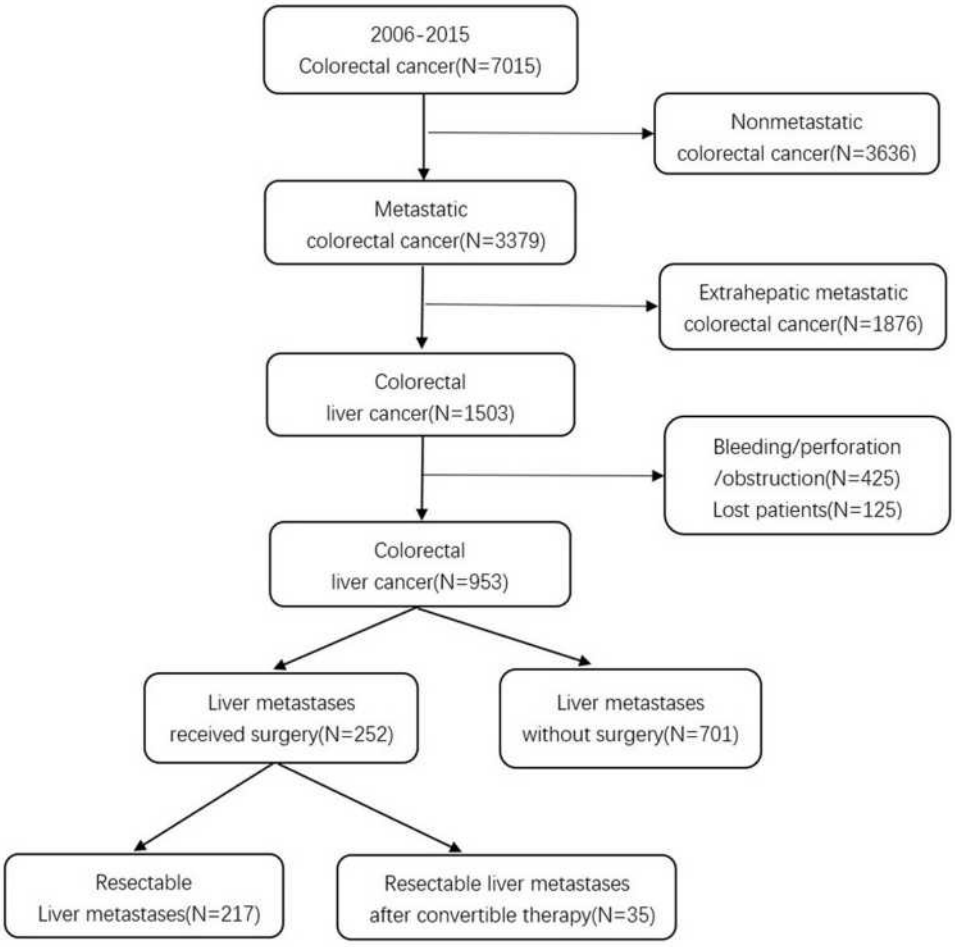

Figure 1 Flowchart of the study. A total of 953 patients with synchronous colorectal liver metastases were included, 252 of them received liver resection and 701 received non-surgical treatment.

Maximum diameter of hepatic metastases: no restriction, 5) R0 resection (macroscopic and microscopic complete resection); 3. No non-resectable extrahepatic metastases.

The indication of primary tumor resection in asymptomatic patients with unresectable liver metastases: no primary tumor-related symptoms, including bleeding, perforation and obstruction.

Follow-Up

All patients with colorectal liver metastases were included in the Surgical Oncology Database of Weifang People's Hospital. Professionals track all patients through outpatient service, telephone or letters, and record the data in the database. The follow-up deadline was April 30th, 2020.

Statistical Methods

All analyses were performed using SPSS software (SPSS for Windows Version 15.0; SPSS Inc, Chicago, IL, USA). Categorical data were compared using Chi square test, and continuous data were compared using independent-samples *t*-test. The 5-year survival rate was calculated using the life-table method, and survival curves were drawn using the Kaplan-Meier method and compared with the Log rank test. P-value <0.05 was considered significant.

Results

Clinical Features of Study Population

Among 953 patients, 316 (33.2%) were rectal cancer, 213 (22.4%) were sigmoid cancer, 72 (7.6%) were left colon cancer, 71 (7.5%) were transverse colon cancer, and 281 (39.3%) were right colon cancer. The majority of patients (N=470, 49.3%) had both right and left lobe involvement, whereas the left and right lobes were involved in 12.6% (N=120) and 38.1% (N=363) of the patients, respectively. In addition, 288 patients (30.2%) had one liver metastasis, 60 (6.3%) had two, 20 (3.1%) had three, and 585 (61.4%) had four or more. The median metastasis size was 4.734 cm. The median serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) before treatment were 228.094 ng/mL and 1078.885 U/mL, respectively.

Survival Followed by Different Surgical Indications for SCLM

Characteristics of Liver Metastases

The proportion of surgical resection margin (<1cm) of hepatic metastases in patients after 2011 was higher than that of patients before 2010 (P<0.001). While, there were no statistically significant differences in the involved hepatic lobe, number of metastatic lesions and the diameter size of liver metastases between the two groups (Table 1).

The Incidence of Complications

Before 2010, the incidence of complications was 23.4% (8/34), including 11.7% (4/34) with hepatic complications and 11.7% (4/34) with systemic complications. The incidence of complications after 2011 was 30.2% (66/218) including 16.9% (37/218) with hepatic complications and 13.3% (29/218) with systemic complications. No significant differences were seen in the incidence of complications between the two groups (P=0.422) (Table 1).

Postoperative Tumor Recurrence

A total of 12 patients (35.2%, 12/34) operated before 2010 experienced tumor recurrence. While, there were 86 patients (39.4%, 86/218) experienced tumor recurrence after 2011. The difference in tumor recurrence rates between the two groups was not statistically significant (P=0.644) (Table 1).

Survival Analysis

The surgical indications for liver metastases between 2006 and 2010 included liver metastases with only one lobe, <4 liver metastases, maximum liver metastasis size <5 cm and a resection margin >1 cm (Table 2). During this period, 250 patients were admitted with median overall survival (OS) of 7.3 months, a hepatectomy rate of 13.6% (34/250) and a 5-year OS rate of 5%.

The expanding surgical criteria for liver metastases between 2011 and 2015 included: complete excision of primary colorectal cancer, complete anatomical resection with negative margins and maintain adequate liver reserve (≥30–50% future liver remnant required), and fit body condition without unresectable extrahepatic metastases (Table 2). During this period, 703 patients were admitted with median OS of 26.3 months, hepatic resection rate of 31.0% (218/703) and a 5-year OS rate of 17%, which were significantly improved compared with that between 2006 and 2010 (P<0.001) (Figure 2A).

Although the hepatectomy rate increased significantly after the expansion of the surgical criteria, the median OS and the 5-year OS rate of patients with liver metastases resection showed no significant differences between 2006–2010 and 2011–2015 (median OS: 43.8 vs 56.1 months; 5-year OS rate: 21% vs 42%, P=0.318) (Figure 2B). However, the median OS and 5-year OS rate of patients with liver metastases non-resection were significantly improved between the two groups (median

Table 1 Characteristics of the Study Patients Who Underwent Liver Surgery

Variable	2006–2010 N = 34	2011–2015 N = 218	Statistical Values	*P*-value
Surgical resection rate of hepatic metastases	13.6% (34/250)	31.0% (218/703)	$\chi2$=17.960	0.000
Gender (Male: Female)	20:14	148:70	$\chi2$=1.088	0.297
Median age (years)	60.82	57.35	t=1.714	0.088
Location of primary cancer			$\chi2$=4.311	0.365
Rectum	8	77		
Sigmoid	7	43		
Left colon	1	13		
Transverse colon	6	19		
Right colon	12	66		
Median serum CEA level (ng/mL)	64.59	114.43	t=-0.996	0.321
Median serum CA19-9 level (U/mL)	183.86	763.86	t=-1.260	0.210
Number of involved lobes			$\chi2$=0.119	0.730
Unilobar	25	154		
Bilobar	9	64		
Number of hepatic metastases			$\chi2$=0.011	0.915
1–3	22	139		
≥4	12	79		
Median diameter of hepatic metastases (cm)	4.09	4.45	t=−0.372	0.710
Resection margin			$\chi2$=107.098	0.000
<1 cm	2	190		
≥1 cm	32	28		
Total complications	8 (23.4%)	66 (30.2%)	$\chi2$=0.645	0.422
Hepatic complications	4 (11.7%)	37 (16.9%)		
Hemorrhage/hematoma	1	4		
Bile leakage	0	5		
Transient hepatic insufficiency	1	16		
Ascites	1	3		
Subphrenic fluid	1	5		
Other	0	2		
Systemic complications	4 (11.7%)	29 (13.3%)		
Pleural effusion	1	11		
Pneumonia/atelectasis	1	7		
Urinary tract infection	1	4		
Other	1	7		
Recurrence rate	12 (35.2%)	86 (39.4%)	$\chi2$=0.214	0.644

Note: values are shown as median (interquartile range), or number (percentages).
Abbreviations: $\chi2$, Chi square test; t, independent-samples *t*-test; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9.

Table 2 Comparison of Different Surgical Indications for Synchronous Colorectal Liver Metastases

Surgical Indications (2006–2010)[3*]	Surgical Indications (2011–2015)[2*]
1. Metachronous hepatic metastases	1. The primary colorectal cancer could be (simultaneous metastases), or has been (metachronous metastases) radically resected
2. Characteristics of hepatic metastases	2. Characteristics of hepatic metastases
	1) Remnant hepatic volume ≥ 30–50%
1) Involving a single lobe	2) Involving multiple lobes: no restriction
2) Number of hepatic metastases <4	3) Number of hepatic metastases: no restriction
3) Maximum diameter of hepatic metastases < 5 cm	4) Maximum diameter of hepatic metastases: no restriction
4) Resection margin >1 cm	5) R0 resection (macroscopic and microscopic complete resection)
3. No extrahepatic metastases	3. No non-resectable extrahepatic metastases

Note:* The significance of the indicator 2 and 3: (1) hepatectomy rate (P<0.001), (2) complications (P=0.422), (3) recurrence rate (P=0.644), (4) the 5-year overall survival rate (P<0.001).

OS: 6 months vs 22 months; 5-year OS rate: 0% vs 5%, P<0.001) (Figure 2C).

Survival After Simultaneous or Staged Resection of Primary Colorectal Cancer and Liver Metastases

In 158 patients with simultaneous resection and 94 patients with staged resection, there was no significant difference in age, sex, the location of the primary tumor, preoperative CEA level, preoperative CA19-9 level and the number of involved liver lobes between the two groups, except for slight difference in the number of liver metastases (P=0.029) and the maximum size of liver metastases (P=0.019).

The total per-patient medical expenses in the simultaneous resection group were reduced by approximately 22.9% compared with that in staged resection group (36,698 RMB vs 45,134 RMB, dollars vs dollars, P<0.001). There were no significant differences in perioperative mortality (2.5% vs 2.1%, P=0.839) and in the complication rate (22.2% vs 19.1%, P=0.572) between the two groups. The median OS and 5-year OS rate of the patients in the simultaneous and staged resection groups were 47.6 and 47.1 months, 34% and 29%, respectively, without significant differences (P =0.948) (Table 3, Figure 3).

Survival After Primary Tumors Resection (PTR) in Asymptomatic Patients with Unresectable Liver Metastases

A total of 736 patients with unresectable liver metastases, including 409 asymptomatic (without bleeding/perforation/obstruction) patients with PTR and 327 without PTR. Compared with patients without PTR, the median OS and the

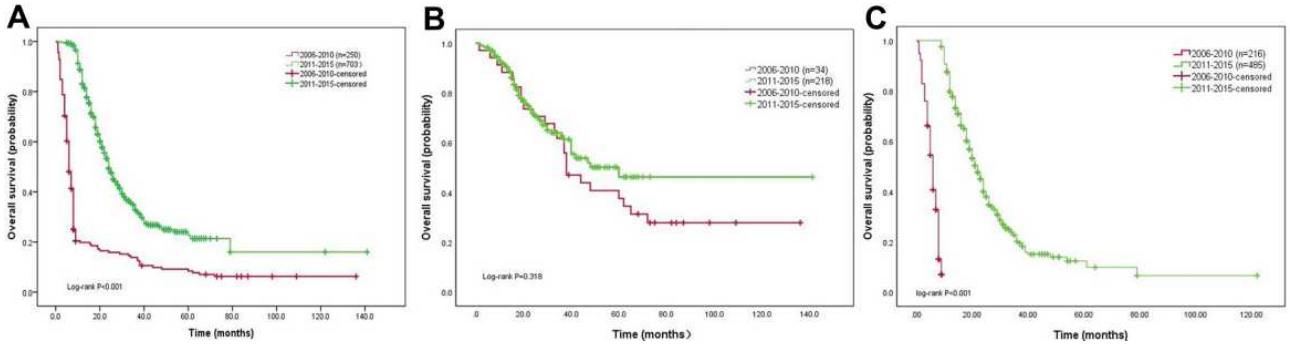

Figure 2 Overall survival of patients with different surgical indications between 2006–2010 and 2011–2015. The overall survival of patients (**A**) with synchronous colorectal liver metastases (**C**) with liver metastases non-resection in 2011–2015 was higher than that in 2006–2010. (**B**) The overall survival of patients with liver metastases resection was no significant difference between 2006–2010 and 2011–2015.

Table 3 Characteristics of Patients Who Received Simultaneous or Staged Resection of Primary Colorectal Cancer and Liver Metastases

Variable	Simultaneous Resection N=158	Staged Resection N=94	Statistical Values	P-value
Sex (male: female)	110:48	58:36	$\chi2$ =1.663	0.197
Median age (years)	58.1 (32–80)	57.2 (28–80)	t=0.624	0.533
Location of primary tumor			$\chi2$ =3.483	0.480
Rectum	51	32		
Sigmoid colon	28	22		
Left colon	10	4		
Transverse colon	15	12		
Right colon	54	24		
Median CEA level (ng/mL)	95.41	124.80	t=−0.823	0.412
Median CA19-9 level (U/mL)	357.33	1050.98	t=−1.936	0.057
Number of lobes involved			$\chi2$ =3.779	0.052
Uni-lobal	119	60		
Bi-lobal	39	34		
Number of hepatic metastases			$\chi2$ =4.772	0.029
1–3	109	52		
≥4	49	42		
Median hepatic metastases size (cm)	4.004	5.397	t=−2.381	0.019
Average medical expense	36, 698	45, 134	t=−1833.624	<0.001
Perioperative mortality	4 (2.5%)	2 (2.1%)	$\chi2$ =0.041	0.839
Complications	35 (22.2%)	18 (19.1%)	$\chi2$=0.320	0.572
Delayed wound-healing	12	7		
Ascites/Infection	10	4		
Transient hepatic insufficiency	3	2		
Anastomotic leakage	3	1		
Pulmonary infection	4	2		
Cardiovascular events	2	1		
Intestinal obstruction	1	1		

Note: values are shown as median (interquartile range), or number (percentages).
Abbreviations: $\chi2$, Chi square test; t, independent-samples *t*-test; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9.

5-year OS rate of the patients with PTR were significantly improved (18.0 vs 15.0 months, 7% vs 3%, P=0.006) (Figure 4).

Prognosis After Different Treatment Strategies for SCLM

The median OS and 5-year OS rate of the 953 SCLM patients were 21.1 months and 12%, respectively. Two hundred fifty-two patients with liver metastases resection had median OS and 5-year OS rate of 47.3 months and 31%, respectively, significantly better than 17.2 months and 4% in those with non-surgical treatment (701) (P<0.001) (Figure 5A). A total of 35 patients with unresectable liver metastases received surgical treatment after convertible therapy, accounting for 5.0% (35/701) of patients with initially unresectable liver metastases, and 13.9% (35/252) of all surgical patients. The median OS and 5-year OS of these 35 patients and 217 patients with initially resectable hepatic metastases

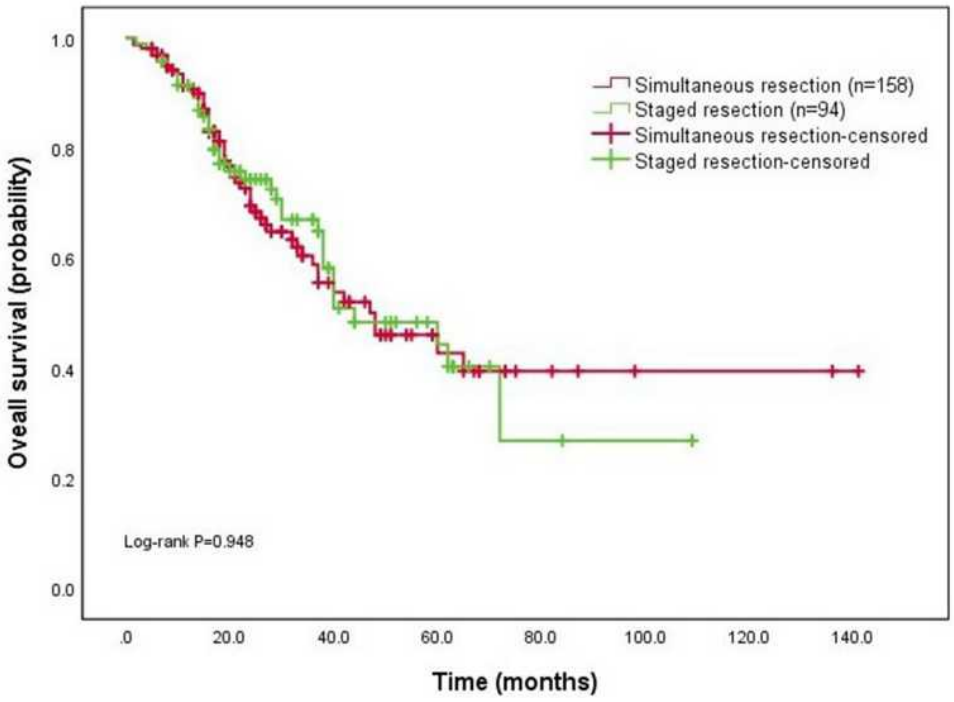

Figure 3 Overall survival of patients with primary colorectal cancer and liver metastases undergoing simultaneous or staged resection. No significant differences could be detected in the overall survival between simultaneous resection group and staged resection group.

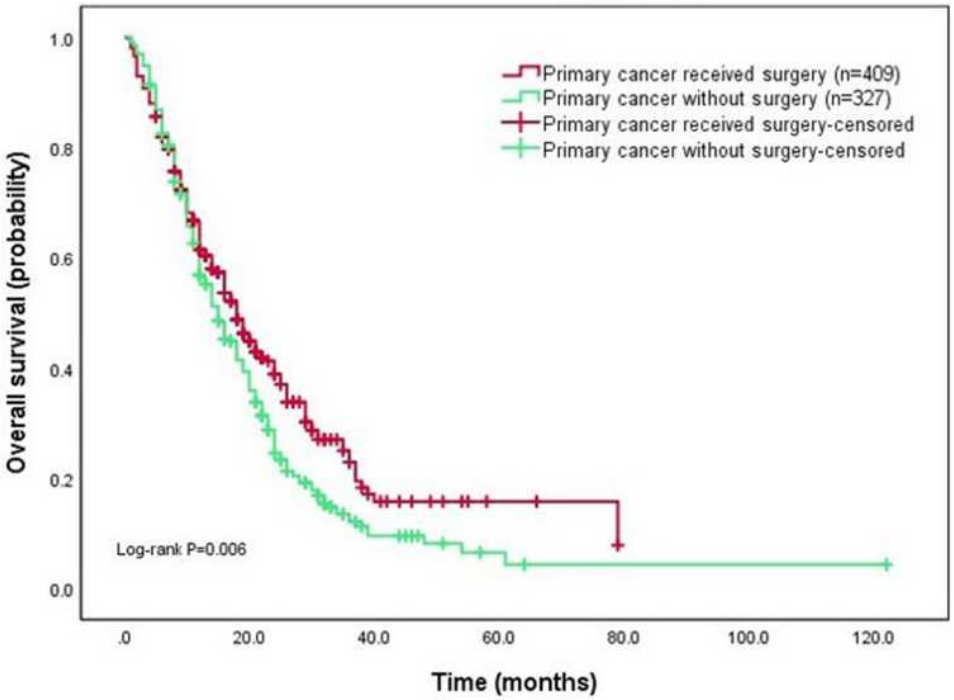

Figure 4 The impact of primary tumor resection on overall survival in patients with asymptomatic colorectal cancer and unresectable liver metastases. Primary tumor resection had better survival compared with those patients without primary tumor resection.

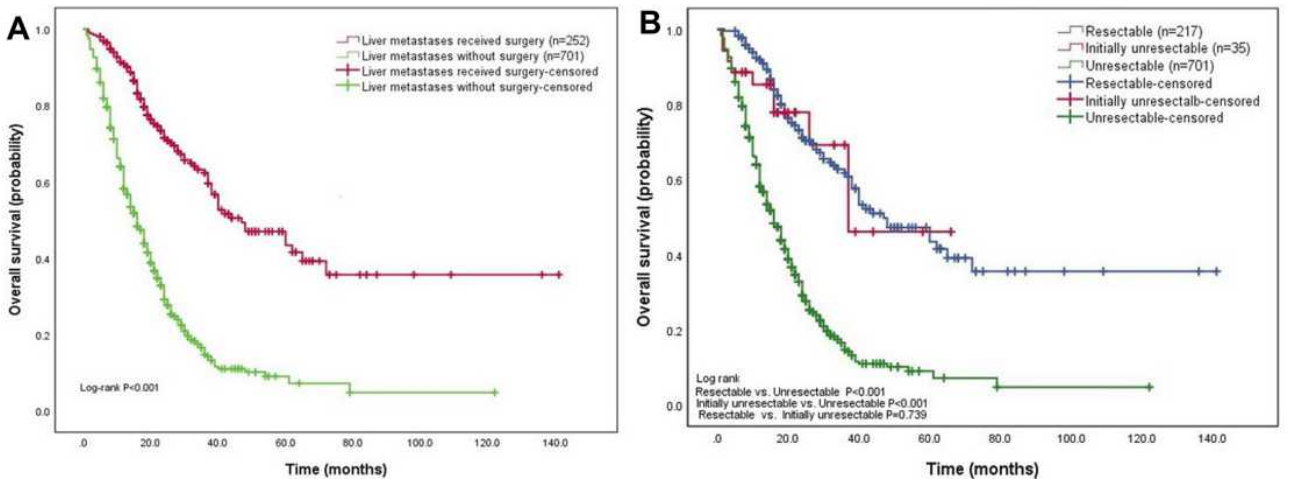

Figure 5 Overall survival of different treatment strategies for liver metastases. (**A**) The survival of patients with liver metastases resection was significantly better than that of patients without liver metastases resection. (**B**) The overall survival of patients with resectable liver metastasis and those with initially unresectable liver metastases were better than those with non-surgical treatment. However, there was no significant difference between patients with initially unresectable liver metastases and those with liver metastasis that could be resected initially.

were 44.2 to 47.8 months and 42% to 31%, respectively, which were all better than those 701 patients with unresectable liver metastases even after systematic therapy (17.2 months, 4%, P<0.001 vs P<0.001). However, there was no significant difference between these 35 patients and patients with liver metastasis that could be resected initially (P=0.739) (Figure 5B).

Discussion

Colorectal cancer has become the third most common malignancy worldwide.[4] At colorectal cancer diagnosis, 20–25% of patients have stage IV disease, in which synchronous colorectal liver metastases (SCLM) are present in 15–25% of cases and metastases are confined to the liver in 70–80% of these cases.[5] The only potentially curative therapy for SCLM is surgical resection,[3,6] which has a median overall survival (OS) of 47.3 months and 5-year OS rate of 31% in our study, which were superior to those with non-surgical treatment (17.2 months, 4%, P<0.001). However, only a minority of patients are suitable for upfront surgery. Therefore, improving the resection rate of SCLM is important. In recent years, an increase in liver metastases resection and utilization of new chemotherapeutics have significantly improved the survival of patients with colorectal liver metastases.[7,8] A retrospective study involving 2470 patients with colorectal liver metastases conducted at two large cancer centers, MD Anderson and Mayo Clinic, found that the median OS increased from 14.2 months during 1990–1997 to 29.2 months during 2004–2006, and the 5-year OS rate increased from 9.1% in 1990–1997 to 19.2% in 2001–2003. The authors attributed profound improvements in outcome to the use of hepatic resection in selected patients during 1998 to 2006 and advancements in medical therapy from 2004 to 2006.[9] A total of 1028 patients with hepatic resection for colorectal hepatic metastases were divided into 2 groups according to the periods before and after the expanding indications for hepatic metastases in a recent research. Perioperative mortality rates, 5-year OS rate and progression-free survival rate did not differ according to treatment period; however, more recently operated patients experienced more postoperative complications. The researchers justified an expansion of the criteria for resectability in that patient category.[10] Our study also showed that after the expansion of surgical indications, the rate of surgical resection rose from 13.6% to 31.0% (P<0.001). However, no significant differences between two groups regarding postoperative recurrence rates (35.2% vs 39.4%, P=0.644) and complication rates (23.4% vs 30.2%, P=0.422) were recorded. Patients were able to obtain favorable short-term mortality and morbidity outcomes without increasing the likelihood of long-term recurrence or any negative effect on survival outcomes, so an expansion of resectability of colorectal liver metastases was justified.

Another fact was that the biggest advance in unresectable SCLM during the past decade was to convert inoperable liver disease to resectable disease using modern agents. Several clinical studies have shown that the association of chemotherapy with bevacizumab and cetuximab

is particularly promising in improving resectability rate and survival.[11] Adam et al[12] reported that 5- and 10-year OS rate of 184 patients with initially unresectable SCLM after combining downsizing chemotherapy and rescue surgery were 33% and 27%, respectively, and 24 patients (13%) were considered cured. Our study found that 35 patients with initially unresectable SCLM underwent hepatic resection after conversion therapy, and a 5-year OS rate of 42% was achieved versus a rate of 4% in patients with unresectable hepatic metastases even after systematic therapy (P<0.001). Therefore, the increased resection of liver metastases and increased utilization of new chemotherapeutics have significantly improved the OS of patients with colorectal liver metastases.

The optimal surgical strategy, whether simultaneous or staged resection of primary colorectal cancer and hepatic metastases, remains obscure for patients with resectable SCLM. A previous study showed that for patients with synchronous rectal liver metastases the complications of simultaneous resection were 58.3%, but only 29.6% of patients underwent staged resection.[13] A study in South Korea also showed that the incidence of postoperative complications was 76.4% in simultaneous resection combined with large-scale hepatectomy, and even as high as 87.0% in large-scale hepatectomy combined with rectal surgery.[14] The latest meta-analysis of 10,848 patients (including 1 prospective and 43 retrospective studies) showed that the simultaneous resection had the highest postoperative severe complications and mortality within 30 days, but the OS was better than the first resection of liver metastases, which is comparable to the group that resected the primary colorectal tumor first.[15] From the above-mentioned literature, it can be seen that the increase of perioperative complications will inevitably delay subsequent therapy, thereby affecting long-term survival. Therefore, simultaneous resection needs to be cautious.

However, a substantial number of studies made the opposite conclusion. A meta-analysis involving 2880 patients indicated that there were no significant differences in OS, recurrence-free survival rate or 60-day postoperative mortality between patients with synchronous hepatectomy and those with staged colorectal hepatic metastases. While, patients with synchronous hepatectomy had lower postoperative complication rate (P=0.0002).[16] Another study pointed out that compared with the staged resection, the operation time of simultaneous resection is shorter [(5.9±1.6) h vs (9.2±2.2) h, P<0.01], and intraoperative blood loss is less [(630±530) vs (1200± 760) mL, P<0.01], and shortened the average postoperative hospital stay [(10 ±5) vs (18±7) d, P<0.01], and did not increase the incidence of postoperative complications and perioperative death rate.[17] A recent meta-analysis included 1203 patients, of whom 748 chose to remove primary colorectal cancer first, 75 chose to remove liver metastases first, and 380 chose simultaneous resection. There was no significant difference in 5-year OS rate and recurrence rate between the 3 groups, and the 5-year OS rate of patients who completed the treatment could reach over 40%.[18] And simultaneous resection can significantly reduce the average length of hospital stay.[19] The present data from our study also showed that there were no significant differences in perioperative mortality (P=0.839), complications (P=0.572) or long-term survival (P=0.948) between the simultaneous and staged resection groups, and the medical costs of the patients with simultaneous resection were reduced by approximately one quarter compared with those of patients with staged resection (P<0.001). Although there was currently no prospective randomized controlled study on the long-term survival of staged resection and simultaneous resection, and most retrospective studies may have data mismatch problems, however simultaneous resection can obviate secondary operations, prevent rapid growth of hepatic metastases after the resection of primary cancer, and reduce medical costs, so it can be conducted in chosen patients.[20]

With the progress of laparoscopy in the field of liver and colorectal cancer, laparoscopic simultaneous hepatectomy and enterostomy have become a safe and effective method due to its advantages of less trauma, mild pain, less intraoperative bleeding and short hospitalization.[21] An international multicenter study involving 142 colorectal liver metastases (CRLM) patients showed that the perioperative mortality and complication rates of CRLM patients undergoing total laparoscopic simultaneous resection were 2.1% and 31.0%, and the 1-,3-, and 5-year survival rates were 98.8%, 82.1%, and 71.9%, respectively.[22] The main results of the OSLO-COMET randomized controlled trial comparing laparoscopic hepatectomy with open hepatectomy revealed that the incidence of Class II and above complications in the laparoscopic group was 19% within 30 days after operation, which was significantly lower than that in open hepatectomy group (31%), Besides, the postoperative hospital stay was shorter.[23] Although the baseline data for these cases were not rigorously matched, it does suggest to some extent that the safety and efficacy of laparoscopic simultaneous resection can be assured for a team of

experienced physicians in a select subset of CRLM patients. However, limited by the location, the number of liver metastases, and the difficulty of resection (such as middle lobe hepatectomy and hemihepatectomy), laparoscopic technology still has certain limitations. A study has confirmed that the conversion to laparotomy in laparoscopic hepatectomy significantly increases the overall complications and the incidence of serious complications in patients. Therefore, if the preoperative evaluation is insufficient, blind application of the total laparoscopic technique may lead to a poor prognosis.[24] Many studies have observed improvements in surgical safety and short-term outcomes, such as lower blood loss, shorter postoperative hospital stays, and declined postoperative complications rate, but these improvements are moderate and not observed in all studies.[25] In addition, in recent years, the application and exploration of laparoscopic radical resection of colorectal cancer combined with open liver metastasis resection in SCLM resection are increasing, but there is a lack of relevant large-sample prospective clinical research.[26] We believe that the laparoscopic technique is limited by the operator's proficiency and the location, number, and size of liver metastases. For the center's lacking experience, the pursuit of minimally invasive surgery may increase the operation time and other injuries, and increase the incidence of perioperative complications. Therefore, when choosing laparoscopic treatment, individual differences should be considered, and indications should be strictly grasped.

For asymptomatic colorectal cancer patients with unresectable liver metastases, there are controversies and consensus in primary tumor resection (PTR). PTR is required to palliate presenting symptoms. Nevertheless, it remains controversial whether up-front PTR is effective for asymptomatic primary tumor. Favorers believe that PTR could prevent tumor-related complications such as bleeding, perforation, and bowel obstruction while create favorable conditions for subsequent chemotherapy. Opponents worry that postoperative recovery and complications would delay the timing of systemic chemotherapy thus increasing risk of disease progression. Therefore, we will discuss the correlation between presence of primary tumor and bowel complications and whether PTR brings survival benefits, so as to explore the best treatment strategy for stage IV colorectal cancer with unresectable metastases. The US NSABP C-10 trial showed that among 86 patients, only 12 (14%) had major morbidity related to intact primary tumor, which was lower than the trial's preset acceptable incidence rate (25%), while 63 (73.3%) patients had no symptoms related to the primary tumor before death or terminating. Therefore, the combination of mFOLFOX6 and bevacizumab did not lead to an unacceptable rate of obstruction, perforation, bleeding, or death associated with intact primary tumor. Surgical resection of asymptomatic intact primary tumor was not compromised.[27] A retrospective cohort study using data from the SEER and NCI databases analyzed 64,157 patients diagnosed with stage IV colon or rectal cancer from 1988 to 2010. Of the 64,157 patients, 43,273 (67.4%) had undergone primary tumor resection. The annual rate of PTR decreased from 74.5% in 1988 to 57.4% in 2010 (P<0.001). Especially since 2001, a trend toward fewer PTR was seen. Median relative survival rate improved from 8.6% in 1988 to 17.8% in 2009 (P<0.001). Despite the decreasing PTR rate, patient survival rates improved. Therefore, the authors conclude that the survival benefit for metastatic colorectal cancer patients does not arise from PTR.[28] A recent Japanese study of JCOG1007 (iPACS) showed that median OS was 25.9 months (95% CI 19.9–31.5) for PTR plus chemotherapy (CTX) and 26.7 (21.9–32.5) for CTX alone (hazard ratio 1.10 [0.76–1.59], one-sided P=0.69). Median progression-free survival (PFS) was 10.4 (8.6–13.4) with PTR plus CTX and 12.1 (9.4–13.2) with CTX alone (hazard ratio 1.08[0.77–1.50]). There were three treatment-related deaths following PTR due to postoperative complications. Therefore, PTR followed by CTX has no survival benefit over CTX alone. PTR is not recommended for colorectal cancer patients with asymptomatic primary tumor and synchronous unresectable metastases.[29]

However, several recent studies supported the idea that palliative resection of the primary tumor is associated with improved OS in incurable stage IV colorectal cancer.[30–33] A French research retrieved individual data of 1155 patients with metastatic colorectal cancer included in four first-line chemotherapy trials and assessed the impact of PTR on OS. Amongst the 1155 patients, 810 patients met the inclusion criteria for analysis and 59% (n = 478) underwent PTR. Compared to patients in the non-resection group (n =3 32 [41%]), PTR was an independent predictor of better OS and PFS in multivariate analysis (HR, 0.63[0.53–0.75]; P<0.001) (HR, 0.82[0.70–0.95]; P<0.001). The studying results demonstrated that PTR independently associated with better survival in patients with colorectal cancer and unresectable synchronous metastases.[34] Thirty-seven thousand and seven hundred ninety-three Stage IV colorectal cancer patients were identified in the Surveillance, Epidemiology, and End Results

between 1998 and 2009. Of those, the majority of patients (23,004, 60.9%) underwent palliative PTR. In Cox regression analysis after propensity score matching PTR was associated with a significantly improved OS (HR=0.40,95% CI= 0.39–0.42, P<0.001) and cancer-specific survival (HR=0.39, 95% CI=0.38–0.40, P<0.001). Therefore, the dogma that an asymptomatic primary tumor never should be resected in patients with unresectable colorectal cancer metastases must be questioned.[35] A systematic review and meta-analysis of MEDLINE/PubMed in Germany was performed, with no language or date restrictions, for studies comparing PTR versus conservative treatment without PTR for metastatic colorectal cancer. Of 37,412 articles identified on the initial screening, 56 retrospective studies with 148 151 patients met the inclusion criteria. PTR led to an improvement in OS, PFS and cancer-specific survival. Neither was the complication risk altered. Therefore, PTR may provide a modest survival advantage in patients with metastatic colorectal cancer.[36] An open-label, prospective, randomized controlled trial (PTR Trial NCT01978249) in South Korea showed that the two-year cancer-specific survival was significantly higher in the PTR group than in the upfront chemotherapy group (72.3% vs 47.1%; P=0.049). However, there was no significant difference in the two-year OS rate between the PTR and upfront chemotherapy groups (69.5% vs 44.8%, P=0.058). The primary tumor-related complication rate of the upfront chemotherapy group was 22.7%. The major complication rate was 3.8% and PTR-related complication rate was 19.2%. The rates of conversion to resectable metastases were 15.3% in the PTR group and 18.2% in the upfront chemotherapy groups. While PTR followed by chemotherapy resulted in better two-year cancer-specific survival than upfront chemotherapy, the improvement in the two-year OS was not significant.[37] Our multidisciplinary team discussed the two randomized trials with opposite opinions (JCOG1007 and PTR Trial) and believed that although the sample size was small, it was very influential. In the light of previous retrospective studies and the experience of our center (the median overall survival: PTR vs CTX, 18.0 months vs 15.0 months, P=0.006), we believed that at present we should be more cautious about whether to recommend PTR, but at the same time, we have more expectations for randomized controlled trials of patients with stage IV incurable colorectal cancer, such as CAIRO-4 (NCT01606098), SYNCHRONOUS (ISRCTN30964555), CLIMAT (NCT02363049), CCRe-IV (NCT02015923), China multicenter (NCT0214978424), GRECCAR 8 (NCT02314182) and hope that when the comprehensive results of these trials are reported in the near future, the role of PTR will be better defined.

Conclusion

For patients with synchronous colorectal liver metastasis, liver metastases resection can improve the overall survival, so we should expand the surgical indications of liver metastases and improve the conversion treatment rate to make more patients get the opportunity of resection; For patients with resectable synchronous colorectal liver metastases, simultaneous resection of the primary tumor and the hepatic metastases which do not increase neither perioperative mortality nor the complication rate in our series and reduce the total per-patient medical expense should be the recommended management; Primary tumor resection for asymptomatic patients with unresectable liver metastases provides benefits in terms of favorable long-term outcomes.

Ethical Statement

This study was approved by the institutional review board of Weifang People's Hospital (the first affiliated hospital of Weifang medical college) and each patient signed an informed consent to authorize their clinical data to be used in future studies. This study was in compliance with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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