Original Article

JHSMR Journal of Health Science and Medical Research

Simultaneous Hepatectomy as a Safe Approach for Synchronous Colorectal Liver Metastasis

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Received 19 March 2020 ● Revised 26 May 2020 ● Accepted 8 June 2020 ● Published online 16 September 2020

Abstract:

Objective: The optimal surgical strategy for treatment of colorectal cancer with synchronous liver metastasis remains controversial. This retrospective analysis compared both surgical and perioperative outcomes for patients receiving simultaneous hepatectomy and primary colorectal surgery, to those receiving hepatectomy alone for stage approach.

Material and Methods: Between; June, 2013 and June, 2019, 111 patients underwent a hepatectomy for synchronous liver metastasis, from this 90 patients received stage resection (hepatectomy alone group), and 21 patients received simultaneous resection (simultaneous resection group) with primary colorectal cancer.

Results: There were no significant differences in gender, age, primary tumor location, tumor size, number of liver metastasis, estimated blood loss, nor rate of blood transfusion. However, the hepatectomy alone group was significantly higher in the proportion of preoperative chemotherapy, compared to the simultaneous resection group (93.3 vs. 38.1%, respectively; p-value<0.001). Additionally, total operative time in the simultaneous resection group was significantly longer, when compared to the hepatectomy alone group (530 vs. 300 minutes, respectively; p-value<0.001). The length of hospital stay was also longer in the simultaneous resection group, compared to the hepatectomy alone group (10 days vs. 7 days, respectively; p-value<0.001). However, the rate of major postoperative complications were similar (14.3 vs. 10.0%; p-value=0.525), respectively. Additionally, major hepatectomy and simultaneous resection were not significantly associated with any major complications.

Conclusion: Simultaneous hepatectomy in synchronous colorectal liver metastasis is a safe approach, and does not increase the risks of major complications.

Keywords: major hepatectomy, simultaneous resection, synchronous colorectal liver metastasis

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J Health Sci Med Res 2021;39(2):115-122
doi: 10.31584/jhsmr.2020764
www.jhsmr.org

Introduction

Liver metastasis in colorectal cancer is one of the factors to determine patient survival. About 15.0-25.0% of patients are usually diagnosed simultaneously with a primary tumor[1]: "synchronous liver metastasis." About 80.0-90.0% of synchronous liver metastasis are non-resectable cases, in which systemic therapy is the mainstay treatment. Long term overall survival can only be achieved in resectable cases, which yield about 40.0-54.0% in five-year survival.[2,3]

There are several surgical strategies for the treatment of resectable synchronous liver metastasis, including staged resection, simultaneous resection and the liver-first approach. Typically, resection of primary colorectal cancer is done first, followed by a stage procedure for liver resection; in order to minimize perioperative complications and avoid delayed systemic chemotherapy, because of simultaneous resection being associated with two major operations conducted during the same operative procedure. This has been considered to be associated with higher morbidity and mortality rates, more so than stage resections. Fortunately, due to the advances of liver surgery in recent decades, the simultaneous resection of primary colorectal tumors and liver metastasis has gained more acceptance. Furthermore, most patients who underwent simultaneous resection did not receive chemotherapy before an operation. Thus, there is less chance of liver injury from hepatotoxic agents.[4] Many authors have reported comparable outcomes in terms of complications and long term survival.[5-7] Moreover, simultaneous resection is associated with a significantly lower, total expenditure.[8]

Although, several studies have demonstrated the safety and efficacy of simultaneous liver resection for synchronous colorectal liver metastasis, many of these studies have a limited number of patients. In this study, we aimed to evaluate the surgical and perioperative outcomes in patients with synchronous liver metastasis, who underwent simultaneous resection, compared to patients who underwent hepatectomy alone for stage approach.

Material and Methods

This retrospective cohort study was conducted in Songklanagarind Hospital, a tertiary care hospital, in southern Thailand. Ethical approval was obtained from the Human Research Ethical Committee. Data were collected from the electronic medical records from all patients. In total, 111 patients were identified from June, 2013 to June, 2019. Liver resection was performed by a single hepatobiliary surgery team. Patients were divided into two groups; according to whether they underwent hepatectomy alone (HA) group (n=90) or simultaneous resection (SR) group, (n=21).

Synchronous liver metastasis was defined as: those identified at the time of diagnosis of primary colorectal cancer. In the simultaneous resection group, the primary colorectal cancer was resected first by the colorectal surgeon team, followed by resection of liver metastasis in the same operative setting. In the hepatectomy alone group, the colorectal cancer was extirpated first, followed by Fluorouracil (5-FU) based standard regimen, systemic chemotherapy or radiation treatment; as indicated. Liver resection was then performed, after 4-6 cycles of chemotherapy, by the hepatobiliary surgeon team.

Liver resections were performed, whether non-anatomical resection or anatomical resection, according to the size and location of the tumors. Intraoperative ultra-sounding was performed in all cases to identify occult metastasis. Parenchymal transection was performed utilizing ultrasonic dissector and electrocautery, with Pringle's maneuver on demand. Patients who had resections combined with intraoperative radiofrequency ablation were included. If the patient had extrahepatic colorectal metastasis, it had to be surgically resectable, and curative intent resection was performed at a later date.

Perioperative morbidity and mortality within 90 days after liver resection were reported, and graded retrospectively according to Dindo-Clavien classification[9] of surgical complications. Severe complications were classified as ≥grade III, and included complications treated with surgical, endoscopic radiologic interventions or death.

All statistical analyses were performed using R program. Categorical variable were compared using Fisher's exact test, and continuous variables were compared using student t-test or Wilcoxon rank-sum test. Statistical significance for all analyses was defined as a p-value <0.050.

Results

Patient and tumor characteristics

From the total of 111 hepatectomy cases for colorectal liver metastasis performed within the study period, patients were either classified into the HA or SR group. The demographic data showed no difference in gender, or age among both groups. The primary tumor location was not different in both groups, with rectal cancer accounting for about 30.0%. The HA group was significantly higher in the proportion of preoperative chemotherapy compared to the SR group (93.3 vs. 38.1%, respectively; p-value<0.001). Additionally, the maximal tumor size and total tumor number were not different in both groups (Table 1).

Table 1 Demographic data

Demographic data	Hepatectomy alone (n=90)	Simultaneous resection (n=21)	p-value
Gender, n (%)			0.576
Male	47 (52.2)	13 (61.9)	
Female	43 (47.8)	8 (38.1)	
Age (years), mean(±S.D.)	61.3 (±11.5)	56.4 (±12.6)	0.087
Tumor location, n (%)			1.000
Colon	60 (66.7)	14 (66.7)	
Rectum	30 (33.3)	7 (33.3)	
Preoperative chemotherapy, n (%)	84 (93.3)	8 (38.1)	<0.001
T stage, n (%)			0.152
T2	2 (2.4)	0 (0.0)	
T3	62 (75.6)	12 (57.1)	
T4	18 (22.0)	9 (42.9)	
N stage, n (%)		0.596	
N0	19 (22.6)	7 (33.3)	
N1	42 (50.0)	9 (42.9)	
N2	23 (27.4)	5 (23.8)	
Preoperative CEA (ng/mL), median (IQR)	12.9 (4.4, 53.9)	11.3 (4.0, 27.5)	0.623
Size of liver metastasis (mm), mean (range)	41.5 (8.0-165.0)	40.1 (7.0-160.0)	0.148
Number of liver metastasis, mean (range)	2.4 (1.0-10.0)	2.4 (1.0-11.0)	0.984

*S.D.=standard deviation, CEA=carcinoembryonic antigen, IQR=interquartile range, ng/mL=nanograms per milliliter

Liver resection and surgical outcome

Types of hepatectomy did not differ in both groups, and wedge resection was the most common type of hepatectomy in both groups, with approximately 71.0 and 54.0% in the HA group and SR group, respectively. The proportions of major hepatectomies were not different in both groups. Hepatectomies performed using the laparoscopic technique in the SR group were higher than those in the HA group, which was statistically significant (33.3 vs. 11.2%, respectively; p-value=0.019) (Table 2). The total operative time in the SR group was significantly longer compared to the HA group (530 vs. 300 minutes, respectively; p-value<0.001). Although, blood loss, packed red cell (PRC) transfusion, and grade of complications were not different among both groups, the length of hospital stay was longer in the SR group compared to the HA group (10 days vs. 7 days, respectively; p-value< 0.001) (Table 2).

Risk factors associated with complication

From a total of 111 hepatectomy cases, one patient from the HA group had died from a suspected myocardial infarction, whilst no mortality cases from the SR group were observed. Forty-six cases developed postoperative complications, ranging from minor to major. Nine patients (10.0%), and three patients (14.3%) from both the HA and SR groups, respectively, developed major complications. There were 2, and 1 patient who suffered from postoperative complications grade 4 and grade 5, respectively; all of these were from the HA group. Two patients had postoperative complications grade 4, which was caused by postoperative liver failure. Meanwhile, no

Table 2 Operative data

Operative data	Hepatectomy alone (n=90)	Simultaneous resection (n=21)	p-value
Type of hepatectomy, n (%)			0.319
Wedge resection	49 (54.4)	15 (71.4)	
Segmentectomy	13 (14.4)	0 (0.0)	
Lateral sectionectomy	3 (3.3)	3 (14.3)	
Anterior sectionectomy	3 (3.3)	0 (0.0)	
Posterior sectionectomy	3 (3.3)	1 (4.8)	
Left hepatectomy	4 (4.4)	0 (0.0)	
Right hepatectomy	9 (10.0)	2 (9.5)	
Extend hepatectomy	3 (3.3)	0 (0.0)	
Trisectionectomy	2 (2.2)	0 (0.0)	
Central hepatectomy	1 (1.1)	0 (0.0)	
Major hepatectomy, n (%)	19 (21.1)	2 (9.5)	0.354
Laparoscopic hepatectomy, n (%)	10 (11.2)	7 (33.3)	0.019
R1 margin*	13 (14.4)	3 (14.3)	1.000
Intraoperative RFA	14 (15.6)	3 (14.3)	1.000
Operative time (min), median (IQR)	300 (210.0, 360.0)	530 (480.0, 720.0)	<0.001
Blood loss (mL), median (IQR)	350 (150.0, 800.0)	400 (200.0, 800.0)	0.799
Blood transfusion, n (%)	20 (23.3)	8 (38.1)	0.267
Hospital stay (day), median (IQR)	7 (6.0, 9.8)	10 (10.0, 13.0)	<0.001

*R1 margin=microscopic margin positive at least one lesion

RFA=radiofrequency ablation, min=minutes, IQR=interquartile range, mL=milliliter liver failure cases were observed in the SR group (Table 3-4).

Table 3 Postoperative complications

Complications	Hepatectomy alone (n=90)	Simultaneous resection (n=21)
Liver specific complication, n (%)		
Liver failure	2 (2.2)	0 (0.0)
Fluid collection/biloma	2 (2.2)	2 (9.5)
Bile leakage	2 (2.2)	0 (0.0)
Transient transminitis	1 (1.1)	0 (0.0)
Non-liver specific complication, n (%)		
Anemia	16 (17.8)	3 (14.3)
Wound complication	2 (2.2)	0 (0.0)
Hematoma	1 (1.1)	0 (0.0)
Gastrointestinal bleeding	1 (1.1)	0 (0.0)
Atelectasis	1 (1.1)	2 (9.5)
Pneumonia	1 (1.1)	0 (0.0)
Pulmonary edema	1 (1.1)	1 (4.8)
Pulmonary embolism	1 (1.1)	0 (0.0)
Pleural effusion	1 (1.1)	1 (4.8)
Delirium	0 (0.0)	1 (4.8)
PDPH	0 (0.0)	1 (4.8)
Gouty arthritis	1 (1.1)	0 (0.0)
Atrial fibrillation	1 (1.1)	0 (0.0)
Myocardial infarction	1 (1.1)	0 (0.0)

*PDPH=postdural puncture headache

Table 4 Complication severity

Complication grade	Hepatectomy alone (n=90)	Simultaneous resection (n=21)	p-value
Complication grade, n (%)			0.919
Grade 1	18 (20.0)	5 (23.8)	
Grade 2	8 (8.9)	3 (14.3)	
Grade 3	6 (6.7)	3 (14.3)	
Grade 4	2 (2.2)	0 (0.0)	
Grade 5	1 (1.1)	0 (0.0)	
Major complication (grade 3-5), n (%)	9 (10.0)	3 (14.3)	0.525

Univariate analysis was performed to identify factors associated with major postoperative complications, and the results are summarized in Table 5. All of these parameters included major hepatectomies, and simultaneous resection, and were not significantly associated with the development of any major complications; therefore, multivariate analysis was not performed.

Discussion

In this present study, simultaneous hepatectomy, with synchronous colorectal surgery, is considered safe as a separate operation. The rate of major complications were similar (14.3 vs 10.0%), respectively. However, the total operative time as well as length of hospital stay were significantly longer for the patients in the simultaneous resection group. Our study also found that major hepatectomy, and simultaneous resection were not significantly associated with major complications. Meanwhile, many reports have shown that severe morbidity after simultaneous resections were higher than staged resections for major hepatectomy.

The concept of simultaneous colorectal liver metastasis surgery was first report in 1991 by Vogt et al.[10], and since then there have been many reports that have demonstrated its safety. Nevertheless, many authors have concerns about the safety and risk of perioperative complications among simultaneous liver resection patients. Recent advances in surgical techniques, preoperative imaging and improvement of perioperative care have increased the safety of simultaneous liver resection, which has resulted in comparable perioperative outcomes along with a significantly lower, total cost of treatment.[8]

Simultaneous resection can be performed either via an open or laparoscopic approach. Additionally, simultaneous laparoscopic colorectal surgery with laparoscopic hepatic resection can be safely performed without increasing the risk of postoperative morbidity, compared

Table 5 Risk factors associated with major complications

Risk factors	Major complication		p-value
	No (n=34)	Yes (n=12)	
Gender, n (%)			0.510
Male	17 (50.0)	8 (66.7)	
Female	17 (50.0)	4 (33.3)	
Age (years), mean (±S.D.)	60.6 (±12.7)	60.7 (±8.4)	0.996
Tumor location, n (%)	0.294		
Colon	22 (64.7)	10 (83.3)	
Rectum	12 (35.3)	2 (16.7)	
Preoperative chemotherapy, n (%)	29 (85.3)	9 (75.0)	0.412
T staging, n (%)			0.778
T2	1 (3.3)	0 (0.0)	
T3	20 (66.7)	6 (60.0)	
T4	9 (30.0)	4 (40.0)	
N staging, n (%)			0.571
N0	9 (29.0)	1 (10.0)	
N1	14 (45.2)	6 (60.0)	
N2	8 (25.8)	3 (30.0)	
Size of liver metastasis (mm), mean (range)	47 (15.0–160.0)	71 (15.0–165.0)	0.506
Number of liver metastasis, mean (range)	3 (1.0–7.0)	4 (1.0–11.0)	0.897
Major hepatectomy, n (%)	9 (26.5)	4 (33.3)	0.717
Operative time (min), median (IQR)	360 (255.0, 467.5)	370 (300.0, 532.5)	0.538
Blood loss (mL), median (IQR)	750 (400.0, 1,175.0)	1,200 (287.5, 2,050.0)	0.335
PRC units, median (IQR)	1 (0.0, 2.0)	2 (0.0,4.0)	0.321
Simultaneous hepatectomy, n (%)	8 (64.7)	3 (25.0)	1.000

S.D.=standard deviation, IQR=interquartile range, mL=milliliter, PRC=packed red cell

to laparoscopic colorectal surgery alone; with carefully selected patients, especially those who require a minor hepatectomy.[11-13] In our study, over 30.0% of the simultaneous group underwent treatment via laparoscopic fashion, which showed no increased risk of major complications.

Major hepatectomies, classified as a hepatectomy with at least three segments, is usually associated with more surgical complications. This is because the liver has usually undergone hepatotoxic chemotherapy. Usually, the liver has some degree of steatosis, or steatohepatitis that may increase surgical complications. Thelen et al. reported that major liver resection increases postoperative mortality in simultaneous resection, and should be avoided.[14] However, most of the reported evidence usually consisted of minor liver resections. Many authors have demonstrated the safety and feasibility of major hepatectomies in simultaneous resection for colorectal metastasis.[15,16] Our study also confirms that a major hepatectomy does not increase perioperative complications, in so saying, there was a limitation, because we only had 9.5% major hepatectomies in the simultaneous group.

A major concern with regards to simultaneous liver resection after neoadjuvant therapy is the hepatotoxic of chemotherapy, at some point. Liver parenchyma injury from preoperative chemotherapy usually occurs in different forms, according to the chemotherapy regimen, which usually increases postoperative complications.[17] The

5-FU base standard regimen has been reported to be correlated with hepatocyte steatosis, and an increase in morbidity and infection-related complications.[18,19] Howbeit, many studies have demonstrated the safety of liver resection after cytotoxic chemotherapy, when conducting proper patient selection. Wu et al.[20] conducted a propensity score matching analysis that showed simultaneous liver resection after chemotherapy did not increase mortality, morbidity, nor did it delay the patient's routine postoperative surgical treatment course. Our study's findings confirmed that preoperative chemotherapy did not increase the risk of major complications.

Rectal surgery is more complicated than colon surgery, and there are limited studies reporting the outcomes of simultaneous liver resection, particularly for rectal surgery. Muangkaew et al.[7] has shown the feasibility and safety of simultaneous resection, focusing on group rectal cancer patients. Among the patients who underwent simultaneous resection for rectal cancer, the complication rate was higher, but there was no difference in major complications. In our study, that consisted of over 30.0% of rectal cancer patients in both the simultaneous and hepatectomy alone groups, showed no difference in the risk of developing major complications as well.

The rationale for separately performing colorectal and liver resections relates to avoiding additional perioperative risk to each other, as in simultaneous resections. Many recent studies consistently report comparable postoperative outcomes between simultaneous and staged approaches. In our study total operative time was significantly longer in the simultaneous group, because it included the operative time of colorectal surgery, and the larger proportion of laparoscopic hepatectomies usually consists of a longer operative time. However, the rate of PRC transfusion, blood loss and proportion of major complications was not statistically different; when compared to the hepatectomy alone group.

Our study has several limitations. First, the surgical approach regarding simultaneous or hepatectomy alone was ultimately made by the personal experience and availability of the surgical team. No selection criteria's were systematically determined or recorded. Second, the proportion of major hepatectomies in both groups might not be high enough to show the effects of major hepatectomies; in terms of surgical complications.

Conclusion

Simultaneous resection for liver metastasis in colorectal cancer surgery should be one of the standard approaches, as it does not increase the risk of major complications. Patient selection criteria for the best outcome when utilizing the simultaneous approach should be determined in the future.

Acknowledgement

The authors would like to thank Miss Nannapat Pruphetkaew for her assistant in data analysis.

Conflict of interest

None

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