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ORIGINAL ARTICLE

Adverse oncological outcome of surgical site infection after liver resection for colorectal liver metastases

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Abstract

Purposes Postoperative complications are associated with poor overall and cancer-specific survival after resection of various types of cancer, including primary colorectal cancer. However, the oncological impact of surgical site infection (SSI) after liver resection for colorectal liver metastases (CLM) is unclear. The aim of this study was to investigate the oncological impact of SSI after liver resection for CLM.

Methods We reviewed data from 367 consecutive patients treated by curative liver resection for CLM between 1994 and 2015. Patients who underwent simultaneous resection of colorectal cancer and synchronous liver metastases ($n=86$) were excluded from the analysis. Short- and long-term outcomes were analyzed.

Results SSI developed in 18 (6.4%) of the 281 patients in the analytic cohort (SSI group). The remaining 93.6% ($n=263$) did not suffer this complication (no-SSI group). The operative duration was significantly longer in the SSI group than in the No-SSI group ($p=0.002$). The overall survival rates 5 years after liver resection for CLM were 33.3% in the SSI group vs. 50.7% in the No-SSI group ($p=0.043$). Multivariate analysis indicated that a liver tumor size ≥ 5 cm, R1 resection, and SSI were independently associated with overall survival after liver resection.

Conclusions SSI after liver resection for CLM is associated with adverse oncological outcomes.

Keywords Surgical site infection · Postoperative morbidity · Liver resection · Colorectal liver metastases · Survival

Introduction

Surgical resection is the gold standard treatment for colorectal liver metastasis (CLM), and the only treatment that can improve the long-term survival of these patients [1–5]. Although liver resection has become safer, with low mortality, in line with improved surgical techniques and perioperative management, morbidity rates remain high. Common complications after liver resection include liver failure, bile leakage, hemorrhage, and infectious disease. Surgical site infection (SSI) is the most frequent complication of liver resection, with an incidence ranging from 2 to 21% [6–8]. Several strategies to reduce the SSI rate have been examined [9–13] and the impact of postoperative complications on the long-term survival of patients with various types of cancer, including primary colorectal cancer and CLM has been investigated [14–21]. However, the specific prognostic impact of SSI after liver resection for CLM remains unclear. The aim of this study was to investigate the oncological impact of SSI after liver resection for CLM.

Patients and methods

Between January 1994 and December 2015, 367 consecutive patients with CLM underwent liver resection, including repeat liver resection, at our institution. Patients who underwent staged resection for synchronous CLM during this period were included in the analysis; however, those who underwent simultaneous resection for colorectal cancer and synchronous liver metastases ($n=86$) were excluded because colorectal surgery is a strong confounding factor for SSI analysis. Demographic, clinical, and pathological data were recorded prospectively and analyzed retrospectively. Major liver resection was defined as the resection of three or more Couinaud's segments.

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Perioperative management

We treated patients with CLM according to the following approach. First, liver resection was attempted regardless of the number or distribution of liver metastases, provided that curative resection would leave sufficient remnant liver (at least 30% of the liver parenchyma). Second, there was no unresectable extrahepatic tumor. In our institution, parenchymal-sparing hepatectomy is a standard policy even for multiple CLMs. Major liver resection was selected only for patients with tumor involvement or contact with the major Glisson's pedicles or hepatic vein.

For tumor staging, contrast-enhanced computed tomography (CT), and ultrasonography were done routinely. Other imaging approaches, including gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) and positron emission tomography (PET), were used for selected patients when necessary. During this period, neoadjuvant chemotherapy was not given routinely. For patients with unresectable recurrent CLM, chemotherapy was performed, and liver resection was planned after reassessment. Radiofrequency ablation was not used in these patients.

Prophylactic antibiotics were given to all patients just before the skin incision and every 3 h during the operation. During laparotomy, exploration and intraoperative ultrasonography (IOUS) of the liver were performed to detect unsuspected liver metastases and to decide on the possibility of resection. Parenchymal transection was performed using either a Cavitron Ultrasonic Surgical Aspirator (CUSA) or Péan forceps, under intermittent total hepatic inflow vascular clamping for 15 min at 3-min intervals. After the resection, the fascia was closed with interrupted absorbable sutures and the wound was closed with continuous absorbable dermis suture.

Postoperative complications were assessed according to the Clavien–Dindo classification system, with complications of grade 3a or worse defined as major [22]. Any complications that developed within 90 days after the operation were included.

Definition of SSI

SSI was defined as incisional infection (either superficial or deep) or organ/space infection. An incisional infection was defined by purulent discharge from the closure site, with or without microbiological evidence. Organ/space infection was defined by radiologic evidence of a fluid collection necessitating drainage, or antibiotic therapy when drainage was difficult. All patients were followed-up by the surgeon for 2–4 weeks after discharge.

Follow-up

All patients were examined every 3 months after liver resection. The follow-up examinations consisted of measuring the serum CEA and cancer antigen 19-9 levels and enhanced CT and/or ultrasonography. Other imaging approaches, including MRI and PET, were done for selected patients when necessary. Postoperative adjuvant chemotherapy was not given routinely following R0 resection, except to patients who were enrolled in a clinical study and required this treatment. Hepatic and extrahepatic recurrences were treated either by surgery when they were resectable or by systemic chemotherapy when they were not.

Statistics

Continuous data are expressed as the median (range). Statistical analyses were performed using Student's *t*-tests, χ^2 tests, and Fisher's exact tests as appropriate. The variables identified as potentially significant by univariate analysis (p value < 0.2) were selected for multivariate analysis with the Cox proportional hazards model to identify independent predictors of survival. A p value < 0.05 was considered indicative of a significant difference. All of the statistical calculations were performed using the IBM SPSS Statistics 21 software package (IBM Japan Inc., Tokyo, Japan).

Results

SSI developed in 18 (6.4%) of the 281 patients included in the analytic cohort, but not in the remaining 263 (93.6%). The median follow-up period was 42 months. The age, sex, body mass index (BMI), American society of anesthesiologists (ASA) status, CEA level, preoperative chemotherapy, primary tumor site, primary tumor lymph node status, synchronous metastases, presence of multiple CLMs, and size of liver metastases did not differ between the groups (Table 1).

Table 2 shows the surgical outcomes in the SSI group vs. the No-SSI group. The major liver resection rate (39% vs. 22%, respectively; $p = 0.144$), total blood loss (650 ml vs. 380 ml, respectively; $p = 0.177$), R1 resection rate (11% vs. 14%, respectively; $p = 1.000$), and mortality rate (5.6% vs. 0.4%, respectively; $p = 0.124$) were similar in the two groups. In contrast, the operative duration was significantly longer in the SSI group than in the No-SSI group (215 min vs. 170 min, respectively; $p = 0.002$). Overall, only one patient, who was from the No-SSI group, suffered another severe infectious complication (postoperative pneumonia).

The overall 5-year survival rates and the median survival times were 33.3% and 22.5 months, respectively, for the SSI

Table 1 Patient characteristics

	SSI ($n=18$)	No-SSI ($n=263$)	P	
Age (year)	60 (35–81)	66 (28–84)	0.088	
Sex (male/female)	12/6	167/96	1.000	
BMI (kg/m^2)	22.9 (17.3–29.1)	21.9 (15.2–37.0)	0.432	
ASA status (I/II/III)	12/6/0	189/73/1	0.853	
CEA (ng/mL)	4.5 (1.1–398.0)	5.7 (0.8–1941.0)	0.833	
Preoperative chemotherapy	1 (6%)	20 (8%)	1.000	
Primary tumor characteristics				
	Primary tumor site (colon/rectum)	14/4	170/93	0.314
	N-positive disease	12 (67%)	167 (63%)	1.000
Liver metastases characteristics				
	Synchronous presentation	3 (17%)	54 (21%)	1.000
	Tumor number (multiple)	9 (50%)	120 (46%)	0.809
	Maximum tumor size (cm)	3.0 (1.2–7.5)	2.5 (0.5–25.0)	0.735

SSI surgical site infection, *BMI* body mass index, *ASA* American society of anesthesiologists, *CEA* carcinoembryonic antigen

Table 2 Surgical outcomes

	SSI ($n=18$)	No-SSI ($n=263$)	P
Major liver resection (≥3 segments)	7 (39%)	58 (22%)	0.144
Laparoscopic resection	0	16 (6%)	0.609
Operative duration (min)	215 (100–546)	170 (40–558)	0.002
Total blood loss (mL)	650 (40–2245)	380 (5–5,080)	0.177
Surgical margin			1.000
	R0	16 (89%)	227 (86%)
	R1	2 (11%)	36 (14%)
Morbidity[a]			
	SSI (incisional/organ space)	7/11	–
	Pleural effusion	1	2
	Refractory ascites	1	2
	Liver failure	1	0
	Other	2	6
Mortality	1 (5.6%)	1 (0.4%)	0.124

SSI surgical site infection

[a]Dindo–Clavien grade ≥ III

group vs. 50.7% and 61.6 months, respectively, for the No-SSI group. There was a significant difference in survival between the groups ($p=0.043$; Fig. 1). According to the analysis in which incisional SSI and organ/space SSI are separated, there was no significant difference in median survival times between these groups (17.8 months for the incisional SSI group vs. 35.5 months for the organ/space SSI group; $p=0.839$).

Multivariate analysis (Table 3) indicated that a liver tumor size > 5 cm (risk ratio 1.70, 95% CI: 1.07 to 2.70, $p=0.026$), R1 resection (risk ratio 1.97, 95% CI: 1.32 to 2.94, $p=0.001$) and SSI (risk ratio: 2.04, 95% CI: 1.15 to 3.64, $p=0.016$) were independently associated with overall survival after liver resection. According to an analysis of the early (1994–2004) vs late (2005–2015) periods within this study, there were 11 (8.9%) SSIs in the early period vs. 7 (5.0%) in the late period. This difference was not significant ($p=0.331$).

Discussion

This study identified an association between long-term survival and the development of an SSI in patients who underwent liver resection for CLM. The overall survival rate was significantly worse for patients with an SSI. Furthermore, SSI was independently associated with overall survival after liver resection for CLM by multivariate analysis.

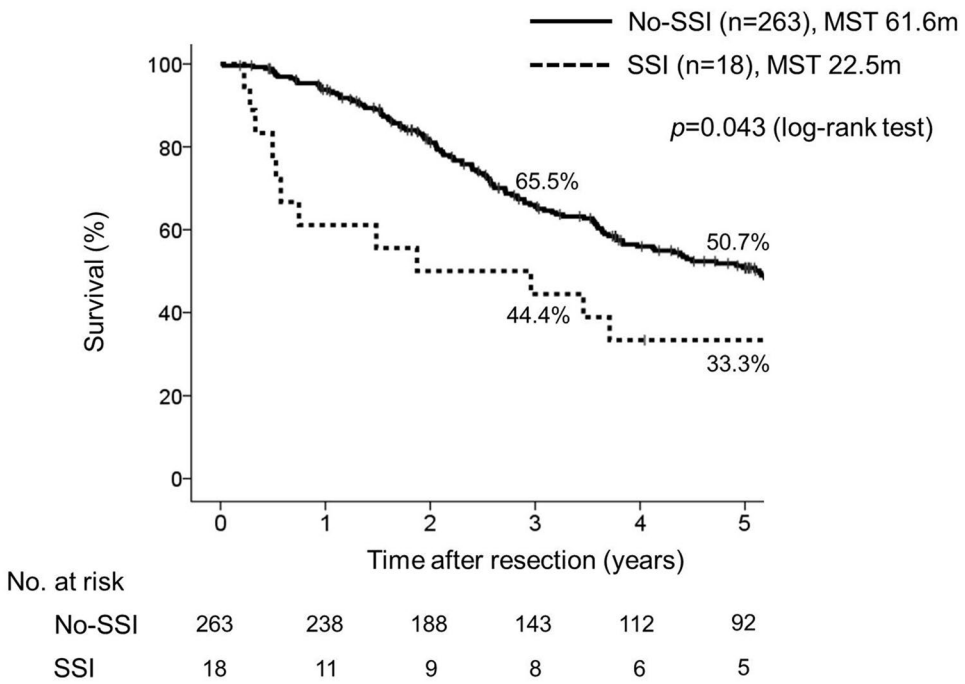

Fig. 1 Overall survival of 281 patients who underwent liver resection for colorectal liver metastases (CLM) according to the presence or absence of a surgical site infection (SSI)

The negative impact of postoperative complications on long-term outcomes has been reported for various cancer surgeries, including those for colorectal, hepatocellular, head and neck, and esophageal cancer [14–17]. Attention has also focused recently on the impact of postoperative complications on the long-term survival of patients undergoing liver resection for CLM [18–21]. The mechanism by which postoperative complications affect long-term survival is not fully understood; however, postoperative complications accelerate the pro-inflammatory response, and subsequent immunosuppression promotes cancer progression [23–25]. Although there are various postoperative complications of liver resection, SSI is representative of infectious complications after surgery.

The incidence of SSI after liver resection has been reported to range from 2 to 21% [6–8]. The risk factors of SSI after liver resection have been studied and high BMI, blood loss, and long operative duration were all significant [26–28]. In this study, the operative duration was significantly longer in the SSI group than in the No-SSI group, but the BMI and blood loss did not differ significantly between the groups. Several authors have reported that the risk of SSI increased with simultaneous liver and colorectal resections [7, 29]. Although simultaneous resection of colorectal cancer and synchronous liver metastases can be performed with a comparable morbidity rate [30], we excluded these patients from the present study. Although rarely performed in liver resection for CLM, hepatectomy with bile duct reconstruction is another risk factor for SSI.

Several strategies have been tried to reduce the SSI rate. Intraoperative peritoneal lavage is performed routinely to minimize peritoneal contamination; however, a recent randomized clinical trial by Tanaka et al., found no significant difference in the rates of SSI between the lavage and no lavage groups. Furthermore, the frequency of organ/space infection was significantly higher in the lavage group. Antibiotic prophylaxis has been recommended to reduce postoperative infectious complications; however, no additional benefit was noted in the incidence of postoperative infectious complications in patients who were given prophylactic antibiotics for an extended period [10]. Furthermore, based on a randomized controlled trial, Hirokawa et al. reported that postoperative antibiotic prophylaxis cannot prevent postoperative infections after liver resection [11]. On the other hand, Hill et al. reported that the implementation of a perioperative infection prevention bundle significantly decreased the overall rate of infections and SSIs, and the postoperative length of stay for patients undergoing liver resection [12]. A case-matched control study by López-Ben et al. showed that laparoscopic liver resection reduces the risk of SSI [8]. Shwaartz et al. demonstrated that drain placement after major hepatectomy may lead to increased postoperative complications including bile leak, superficial surgical SSI, and hospital length of stay [13]. Thus, further investigations to reduce the risk of SSI and improve therapeutic outcomes are warranted.

This study was limited by its single-center, retrospective design, which rendered the outcome data more susceptible to the individual surgical skills and performance of surgeons within the center. In addition, it is unknown whether the relationship between SSI and long-term prognosis is direct or related to the patient's own immunity.

Table 3 Univariate and multivariate analyses for overall survival after liver resection in 281 patients

Variable	*n*	Overall Survival 3-years (%)	5-years (%)	Multivariate Univariate, *p*	Risk ratio (95% confidence interval)	*P*
Age (year)				0.151		0.324
	< 70	190	67.3	51.7		1
	≥ 70	91	57.9	45.5		1.19 (0.84–1.70)
Sex				0.864		
	Male	179	64.8	48.3		
	Female	102	63.0	53.0		
CEA (ng/mL)				0.002		0.173
	< 50	251	66.8	53.4		1
	≥ 50	30	43.3	20.8		1.41 (0.86–2.29)
Primary tumor site				0.468		
	Colon	184	62.1	48.3		
	Rectum	97	68.0	52.1		
Primary nodal status				0.025		0.130
	Negative	102	72.6	59.2		1
	Positive	179	59.8	44.6		1.32 (0.92–1.90)
Number of liver metastases				0.394		
	< 4	217	65.9	52.0		
	≥ 4	64	57.9	41.0		
Size of largest metastases (cm)				0.001		0.026
	< 5	247	67.0	52.1		1
	≥ 5	34	43.6	31.2		1.70 (1.07–2.70)
Type of liver resection				0.979		
	Minor	216	65.4	49.8		
	Major (≥ 3 segments)	65	60.4	48.3		
Curability				< 0.001		0.001
	R0	243	66.3	54.0		1
	R1	38	51.2	25.6		1.97 (1.32–2.94)
Preoperative chemotherapy				0.006		0.084
	Absent	260	65.8	51.5		1
	Present	21	37.1	18.6		1.80 (0.92–3.49)
SSI				0.043		0.016
	Absent	263	65.5	50.7		1
	Present	18	44.4	33.3		2.04 (1.15–3.64)

SSI surgical site infection, *CEA* carcinoembryonic antigen

Other general risk factors of SSI, such as nutritional status, diabetes mellitus, steroid use, and smoking could not be analyzed in detail. Furthermore, the effect of preoperative chemotherapy on the risk of SSI was not analyzed. Although past reports on liver resection and SSI included simultaneous resection for colorectal cancer and synchronous liver metastases, these cases were excluded from the present study to minimize the heterogeneity of the measured variables. Large multicenter series studies to evaluate the oncological impact of SSI after liver resection for CLM would overcome some of the limitations of this study.

In conclusion, the onset of SSI after liver resection is associated with poorer long-term outcomes for patients with CLM. Establishing how to further reduce the risk of SSI is a future task for liver surgeons with a multidisciplinary team.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to disclose.

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