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Risk Factors for Adhesive Small Bowel Obstruction After Liver Cancer Surgery

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Abstract. *Background/Aim: Although the frequency of small bowel obstructions after liver surgery is generally considered low, previous studies have followed-up patients for less than a year, thus the incidence of small bowel obstructions several years after surgery is unknown. Furthermore, the rise in laparoscopic surgeries and the use of adhesion prevention materials may influence the occurrence of small bowel obstructions. This study aimed to assess the incidence of small bowel obstructions within a five-year period following liver surgery and identify the associated risk factors. Patients and Methods: This case series analysis analyzed patients who underwent liver surgery between April 2012 and March 2014 from 32 participating hospitals. Multivariate analysis was conducted to examine risk factors for small bowel obstructions. Results: A total of 953 patients were included in the analysis, and the incidence of small bowel obstructions was 1.6%. The incidence was significantly higher at 3.4% for surgeries related to metastatic liver cancer compared to other types of surgeries. Laparoscopic surgery had no significant effect on the incidence of SBO (p=0.72). There was no significant difference in the incidence of small bowel obstructions between surgeries that employed adhesion prevention materials and those that did not. Multivariable analysis revealed that longer surgical time and re-operation were independent risk factors for small bowel obstructions. Conclusion: The incidence of small bowel obstructions following surgery for metastatic liver cancer is significantly higher compared to other liver surgeries. Neither laparoscopic surgery nor adhesion prevention materials reduce its occurrence. Longer surgical time and re-operation are independent risk factors for small bowel obstructions.*

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Key Words: Small bowel obstruction, laparoscopic surgery, adhesion prevention material, morbidity.

In recent years, the safety of abdominal surgery has improved, leading to a decrease in the incidence of early postoperative complications. However, small bowel obstruction (SBO) can occur as much as several years after surgery, which significantly reduces the quality of life for many patients (1). SBO is a common complication after colorectal or gastric surgery (2). Although the occurrence of SBO after liver surgery is generally considered low, previous studies have observed patients for less than a year, leaving the incidence of SBO several years after surgery unknown. Since only 30-40% of all SBOs occur within the first year after surgery (3, 4), long-term observation is necessary to accurately determine the incidence of SBO.

In recent years, there has been an increase in liver laparoscopic surgery and its safety is well established (5, 6). In patients undergoing liver resection for colorectal metastases, laparoscopic surgery has been associated with significantly fewer postoperative complications compared to open surgery (7). Additionally, laparoscopic colorectal surgery has been reported to reduce the incidence of SBO compared to open surgery (8). A randomized controlled trial also found that laparoscopic distal gastrectomy resulted in fewer SBOs compared to open surgery (9). However, it remains unclear whether laparoscopic liver surgery reduces the incidence of SBOs.

Since 2000, the use of adhesion prevention materials (APMs) has also become increasingly common. Several studies, including our own (10), have reported the effectiveness of APMs in preventing adhesions (11, 12). However, there is no clear evidence that APMs decrease the incidence of SBOs after liver surgery. Previous reports have mainly focused on SBOs after colorectal surgery, and there is some controversy regarding the effectiveness of APMs for SBO prevention (13, 14). Additionally, a randomized clinical trial has found that APMs did not significantly reduce SBO incidence in patients who underwent gastrectomy for gastric cancer (15).

The purpose of this study was to determine the incidence of SBO within five years after liver surgery, as well as to identify its associated risk factors. To address the limitations of previous studies that employed relatively short observation periods, we set a five-year observation period to accurately evaluate the incidence of SBOs after liver surgery and to avoid underestimating their occurrence. Given the improved survival rates of patients undergoing liver surgery, it is increasingly important to understand the incidence of SBO and its related risk factors.

Patients and Methods

This was a case series analysis conducted by the Japanese Society for Abdominal Emergency Medicine, using a standardized data collection sheet. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local institutional review board (Approval No. 20-01-887). This study included patients who underwent liver surgery between April 2012 and March 2014 at 32 participating hospitals. Information regarding the right to opt-out was posted on the website of each hospital. We have previously reported that laparoscopic surgery reduces the incidence of SBO after gastroduodenal or colorectal surgery, but it does not reduce the incidence in other digestive surgeries including hepatobiliary-pancreatic surgery. Additionally, APM does not reduce the incidence of SBO in digestive surgeries (3). The present study aimed to clarify whether laparoscopic surgery or APMs reduce SBO and to identify risk factors associated with SBO, with a focus on liver surgery. We defined SBO as occurring in patients who experience abdominal pain and require hospitalization and fasting, and who have undergone a CT scan to confirm the absence of malignancy recurrence. Ileus was defined as a temporary cessation of normal intestinal motility without a mechanical obstruction. We collected data on patients' disease names, surgical procedures (laparoscopic or open surgery), use of APMs, amount of intraoperative bleeding, surgical time, use of prophylactic drainage, development of ileus, abdominal abscess, and whether the patient developed bowel obstruction within five years after surgery. Currently, three types of APMs, Seprafilm®, Interceed®, and AdSpray®, are available in Japan. However, during the study period, Interceed® (approved in June 2017) and AdSpray® (approved in June 2016) were not yet approved for use in digestive surgery. Our study followed CARE guidelines.

Statistical analysis. Efficacy of laparoscopic surgery and APM use were analyzed using χ^2 tests. Variables included in the multivariable analysis were open surgery, APM use, intraoperative bleeding [with a cut-off value obtained from the receiver operating characteristic (ROC) curve], surgical time (with a cut-off value obtained from the ROC curve), prophylactic drainage, re-operation, abscess formation, and ileus. All statistical analyses were performed using SPSS ver. 24 Base System (SPSS Japan, Tokyo, Japan), and the significance level was set at 5%.

Results

Out of 1,101 patients registered, those with insufficient data were excluded, leaving 953 patients (1.6%) for analysis. Among them, 15 patients (2 hepatocellular carcinomas, 8 metastatic liver cancers, 2 cholangiocarcinomas, 1 gallbladder cancer, 1 non-neoplastic disease, 1 benign liver tumor) developed SBOs, resulting in an overall incidence of 1.6%. Of eight patients with metastatic liver cancers, seven underwent colorectal surgery and one underwent gastrectomy prior to liver surgery. After excluding patients with rare diseases, such as gallbladder cancer, non-neoplastic disease, and benign liver tumors, we found that the incidence of SBO following surgery for metastatic liver cancer (3.4%) was significantly higher than that for hepatocellular carcinoma and cholangiocarcinoma (p=0.02, Table I). There was no significant difference in the incidence of SBO between major surgeries (hemi-hepatectomy and 2 or 3 sectionectomies) and non-major surgeries (p=0.78).

Table I. *Patient's background*.

	N=953	
Age median (Range)	69 (29-89)	%
Men: Women	626: 328	65.6:34.4
Laparoscopic surgery	188	19.7
Use of APM	378	39.6
Amount of bleeding (ml, median)	651	
Surgical time (min, median)	346	
Use of prophylactic drain	736	77.2
Re-operation	29	3.0
Abscess	76	8.0
Ileus	20	2.1
Details of disease		
Hepatocellular carcinoma	462	48.4
Metastatic liver cancer	235	24.6
Cholangiocarcinoma	135	14.2
Gallbladder cancer	50	5.2
Non-neoplastic disease	44	4.6
Benign liver tumor	27	2.9
Major surgeries	253	26.5
Non-major surgeries	700	73.5

APM: Adhesion prevention material.

One-hundred and eighty-eight patients (19.7%) received laparoscopic surgery. Table II illustrates differences in the backgrounds of laparoscopic and open surgery. APM use rate with open surgery (45.3%) was significantly higher than that of laparoscopic surgery (23.9%, $p<0.001$). The amount of bleeding during laparoscopic surgery was significantly lower than that during open surgery ($p<0.001$) and the laparoscopic surgical time was significantly shorter than that of open surgery ($p<0.001$). Incidence of re-operation after laparoscopic surgery was also significantly lower than after open surgery ($p=0.045$), as was the rate of postoperative abscess formation; however, the latter difference was not significant ($p=0.10$). Among all patients, laparoscopic surgery did not reduce the incidence of SBOs (2.1% for laparoscopic and 1.4% for open surgery, $p=0.72$), and it also had no effect on individual diseases (Table III). APMs were used in 378 patients (39.6%). The APM use rate was lowest in non-neoplastic disease ($p=0.002$). There was no significant difference in the incidence of SBOs after surgery with or without APMs ($p=0.10$). No beneficial effect of APMs was observed in any type of disease. In both laparoscopic surgery ($p=0.07$) and open surgery ($p=0.66$), use of APMs did not prevent SBOs (Table IV). Multivariable analysis revealed that longer surgical time (odds ratio=4.44, 95% confidence interval=1.28-15.37) and re-operation (odds ratio=9.18, 95% confidence interval=1.80-46.73) were independent risk factors for SBOs after liver surgery (Table V).

Discussion

This case series analysis included 953 patients who underwent liver surgery, and long-term observations were conducted. To the best of our knowledge, this is the first report regarding the incidence of SBO after liver surgery over a year. We present three important findings. First, despite the large size of the incision, the incidence of SBOs after liver surgery was relatively low, consistent with previous reports. However, the incidence of SBOs following liver surgery for metastatic liver cancer was not negligible. Second, laparoscopic surgery and APMs did not reduce the incidence of SBOs. Third, longer surgical time and re-operation were identified as risk factors for SBOs.

Even with a long-term observation, the incidence of SBO after liver surgery was low, but potentially higher than that reported previously. Fretland *et al*. reported that 2 of 144 patients (0.14%) experienced SBOs within 30 days after liver surgery (7). In the present study, the incidence rate of SBOs was 1.6%, which is 10 times higher than that in Fretland's study. This indicates that a long period of observation is needed to determine the true incidence of SBOs. In our previous report, we demonstrated cumulative incidence rates of SBOs within 1 month, 6 months, 1 year, 3 years, and 5 years at 8.3%, 21.4%, 29.7%, 48.1%, and 59.7%, respectively. Furthermore, 40.3% of SBOs developed more than five years after surgery (3). Assuming, as in our study, that the incidence within one month after surgery accounted for 8.3% of all cases, the calculated incidence within five years in Fretland's study is approximately 1.0%. While many recent papers have reported on short-term outcomes of laparoscopic liver surgery (16-19), few studies have focused on long-term complications after liver surgery.

The incidence of SBOs following surgery for metastatic liver cancer (3.4%) was significantly higher than that for hepatocellular carcinoma and cholangiocarcinoma. This notable incidence is comparable to the incidence after laparoscopic colorectal surgery (3). Considering that all patients with metastatic liver cancer who developed SBOs after liver surgery had previously undergone colorectal or gastric cancer surgery, it is plausible that surgeries involving the gastrointestinal tract may contribute to the occurrence of SBOs. Therefore, it is crucial to be cautious about the presence of adhesions from prior gastrointestinal surgeries when performing liver surgery for metastatic liver cancers.

Superiority of laparoscopic surgery has been reported in various types of surgery, and it was expected to be useful in preventing SBOs. A large population study showed that the 5-year incidence of SBOs was higher with open surgery than with laparoscopic surgery for various procedures, such as Roux-en gastric bypass, partial colectomy, appendectomy, and hysterectomy (20). However, the SBO incidence of liver surgery is relatively low, which means that the reduction in

Table II. *Comparison of patient's background between laparoscopic surgery and open surgery.*

	Laparoscopic surgery (n=188)		Open surgery (n=765)		*p*-Value
	Number	%	Number	%	
Use of APM	45	23.9	333	43.5	<0.001
Amount of bleeding (ml average)	432		1101		<0.001
Surgical time (min average)	324		374		<0.001
Prophylactic drain	146	77.7	590	77.1	0.87
Re-operation	1	0.5	28	3.7	0.045
Abscess	9	4.8	67	8.8	0.10
Ileus	3	1.6	17	2.2	0.80

APM: Adhesion prevention material.

Table III. *Comparison of small bowel obstruction (SBO) rates between laparoscopic and open surgery.*

		Incidence of SBO after laparoscopic surgery		Incidence of SBO after open surgery		*p*-Value
	Number	Number	%	Number	%	
All	953	4	2.1	11	1.4	0.72
Hepatocellular carcinoma	462	0	0	2	0.5	0.90
Metastatic liver cancer	235	3	7.5	5	2.6	0.28
Cholangiocarcinoma	135	0	0	2	1.7	0.62
Gallbladder cancer	50	0	0	1	2.1	1.0
Non-neoplastic disease	44	1	5.9	0	0	0.39
Benign liver tumor	27	0	0	1	6.7	1.0

Table IV. *Comparison of small bowel obstruction (SBO) rates between patients with adhesion prevention material (APM) and those without.*

		Incidence of SBO APM (+)		Incidence of SBO APM (–)		*p*-Value
	Number	Number	%	Number	%	
All	953	9	2.3	6	1.0	0.10
Hepatocellular carcinoma	462	1	0.6	1	0.3	0.66
Metastatic liver cancer	235	7	6.9	1	0.8	<0.001
Cholangiocarcinoma	135	0	0	2	3.1	0.44
Gallbladder cancer	50	0	0	1	3.6	1.0
Non-neoplastic disease	44	1	11.1	0	0	0.20
Benign liver tumor	27	0	0	1	6.7	1.0

SBO incidence resulting from the use of laparoscopic surgery may be small. Pedersen *et al*. also reported that 7 out of 208 (3.3%) patients who received open liver surgery experienced SBOs, compared to no cases of SBO among patients (0/79) who received laparoscopic liver surgery, and there was no significant difference between the two groups (21). Similarly, our study, which included a larger number of cases, found no difference in the incidence of SBO between laparoscopic and open liver surgery (2.1% for laparoscopic and 1.4% for open surgery, $p=0.72$).

The present study found that APMs do not prevent SBOs in liver surgery, as indicated by both univariable and multivariable analyses. While a meta-analysis suggested that APMs are effective in reducing the incidence of SBO, none of the nine studies included in that analysis involved patients who underwent liver surgery (14). One historical control

Table V. *Multivariable analysis of risk factors for small bowel obstruction.*

	Odds ratio	95%CI	*p*-Value
Age	0.97	0.93-1.01	0.12
Sex	0.66	0.21-2.01	0.46
Laparoscopic surgery	1.42	0.40-5.08	0.59
APM	2.85	0.92-8.77	0.07
Bleeding	0.36	0.09-1.46	0.15
Surgical time	4.44	1.28-15.37	0.02
Prophylactic drain	2.55	0.31-20.82	0.38
Re-operation	9.18	1.80-46.73	0.01
Abscess	0.00	0.00	0.99
Ileus	3.28	0.33-32.89	0.31

APM: Adhesion prevention material.

study showed that APMs reduced early postoperative SBO incidence after gastrointestinal surgery; however, the observational period of that study was too short (within 30 days after surgery) (9). An RCT including 1,791 patients showed that APMs did not reduce incidence of SBOs, but significantly reduced the incidence of SBOs requiring reoperation (22). Based on previous studies that have shown that APMs can reduce adhesion (10, 11, 23), it is likely that the primary benefit of APMs in liver surgery is to prevent difficulties during re-operations for recurrent disease by preventing formation of adhesions (24), rather than preventing SBOs.

The present study identified longer surgical time and re-operation as risk factors for SBOs after liver surgery. While re-operations have been identified as significant risk factors for SBOs after gastroduodenal or colorectal surgery (3), there are no previous studies on the relationship between re-operation after liver surgery and SBOs. It is reasonable to assume that re-operation can cause severe adhesions, which could increase the risk of SBOs. Previous studies have not identified whether longer surgical time is a risk factor for SBOs or whether APMs are effective in preventing SBOs in patients undergoing lengthy liver surgeries. The present study suggests that APMs may be useful to prevent SBOs in patients who underwent lengthy surgeries.

Study limitations. First, because this was a case series analysis, some patients had to be excluded due to insufficient data. Second, the present study suffered from a large selection bias, which limited the evaluation of the efficacy of laparoscopic surgery and APMs. During the study period (April 2012 and March 2014), laparoscopic liver surgery was performed only at a limited number of hospitals. This may have contributed to the shorter surgical times observed in laparoscopic surgery compared to open surgery. Third, this study did not include data on blood examinations or treatment for SBOs. Fourth, information on past abdominal surgeries was also lacking. Finally, this study only involved 15 patients who experienced SBOs.

In conclusion, the incidence of small bowel obstructions after surgery for metastatic liver cancer is significantly higher compared to other liver surgeries. Both laparoscopic surgery and adhesion prevention materials do not reduce its occurrence. Longer surgical time and re-operation are independent risk factors for small bowel obstructions.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conception and design: Takeshi Yamada, Daisuke Ichikawa, Norio Yukawa, Toru Aoyama, Kozo Kataoka, Takeshi Shioya, Toshihisa Tamura, Rai Shimoyama, Atsuko Fukazawa, Kensuke Kumamoto, Naoyuki Yamashita, Suguru Hasegawa, Shuji Saito, Ichiro Takemasa, Masaki Kaibori, Nobuhiko Taniai. Acquisition of data: Norio Yukawa, Kozo Kataoka, Takeshi Shioya, Toshihisa Tamura, Rai Shimoyama, Atsuko Fukazawa, Kensuke Kumamoto, Naoyuki Yamashita, Shuji Saito, Masato Yoshioka. Analysis and interpretation of data: Takeshi Yamada. Writing, review, and/or revision of the manuscript: Takeshi Yamada, Toru Aoyama. Study supervision: Hiroshi Yoshida.

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