Significance of bacterial culturing of prophylactic drainage fluid in the early postoperative period after liver resection on the development of surgical site infections

Running title: *Culturing of prophylactic drains after liver resection*

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Abstract

Background: The relation between bacterial culturing of drainage fluid in the early postoperative period after liver resection and development of surgical site infections (SSI) are largely unknown. We evaluated the diagnostic value of the bacterial culturing of drainage fluid on postoperative day (POD) 1 after liver resection.

Methods: The cases of all consecutive patients who underwent elective liver resection from January 2014 to December 2016 were analyzed. The association between a positive drainage fluid culture result of POD1 and the development of SSI was analyzed.

Results: A total of 195 consecutive patients were studied. Positive drain cultures were obtained in 6 patients (3.1%). Multivariate analysis revealed that the positive drain culture was an independent risk factor for SSI (Odds ratio: 8.04, P=0.035). Combined resection of the gastrointestinal tract was a risk factor for a positive drain culture (P=0.006). Among the patients who did not undergo procedures involving the gastrointestinal tract, there was no association between drain culture positivity and SSI.

Conclusion: The detection of positive drainage fluid culture results of POD1 after liver resection was associated with SSI. However, among patients who did not undergo procedures involving the gastrointestinal tract, it was not a predictor of SSI.

Introduction

Advances in surgical and perioperative management techniques have reduced the morbidity and mortality rates seen after liver resection (1, 2). However, the incidence of bile leakage after liver resection still ranges from 3.6% to 12%, and the post-liver resection incidence of organ/space surgical site infections (SSI) ranges from 4.0% to 10.5% (3-5). Therefore, they remain serious clinical problems. The ability to detect bile leakage or SSI early might improve the safety of liver resection.

Some studies have reported that prophylactic abdominal drainage is not recommended after liver resection because it increases the risk of retrograde infections, ascitic fluid leakage, vascular injuries, and intestinal ulceration (6-8). However, in liver resection prophylactic drains have been used to facilitate the early detection and treatment of complications, such as hemorrhaging and bile leakage (9, 10). On the other hand, prolonged drain placement after liver resection is associated with drain fluid infections, including retrograde infections (10, 11). To prevent retrograde infections, unnecessary drains should be removed as soon as possible, and so reliable criteria for drain removal are required. We have reported that the early removal of prophylactic drainage tubes after liver resection based on the bilirubin concentration of the drain discharge on POD 3 is safe (12). However, in this study some patients developed organ/space SSI after drain removal. Therefore, predictors of organ/space SSI after liver resection are needed.

Regarding gastrectomy, it was reported that the detection of positive bacterial cultures of the drainage fluid on POD 1 was an independent predictor of intra-abdominal abscess formation (13). Also, it was demonstrated that intraoperative bacterial contamination of the abdominal cavity had an adverse impact on the risk of SSI after pancreaticoduodenectomy (14). Thus, we hypothesized that the detection of positive drainage fluid culture results during the early postoperative period might be associated with the development of SSI. No previous studies have focused on the relationship between the results of bacterial cultures of drainage fluid conducted on POD 1 and postoperative complications after liver resection. The aim of this study was to determine whether the results of bacterial cultures of drainage fluid obtained on POD 1 after liver resection are associated with the development of SSI.

Method

Study population

All consecutive patients who underwent elective liver resection followed by prophylactic abdominal drain insertion at the Department of Surgery, Nara Medical University, between January 2014 and December 2016 were included in this retrospective study. Prophylactic drainage was performed after liver resection in all patients. Drains were placed near to each cut surface of the liver. Bacterial culturing of the drain discharge was conducted on POD 1 in all cases.

Surgical procedures

Major hepatectomy was defined as the resection of three contiguous segments according to Couinaud's classification. Anatomical resection included segmentectomy, sectionectomy, hemi-hepatectomy, and tri-sectionectomy. The surgical procedure was performed as described previously (12, 15, 16). Parenchymal transection was carried out using the clamp-crushing method or the Cavitron ultrasonic surgical aspirator combined with blood inflow occlusion. Fibrin glue was applied to the liver surface after parenchymal transection. Lavage of the cut surface of the liver and the intra-abdominal cavity were performed using over 3 liters of saline. A silicon rubber closed drain (SILASCON® Duple drain; KANEKA MEDICAL PRODUCTS, Tokyo, Japan) was routinely placed near to each cut liver surface. Abdominal wall closure was carried out using interrupted absorbable monofilament sutures (PDS-II). The incisional wound was irrigated with 1 liter of saline. Skin closure was achieved using intradermal sutures and an absorbable monofilament needle. Routine cefazolin (1 g)-based prophylactic antibiotic therapy was administered before surgery and every 3 hours during the operation. It was also administered 6 hours after the liver resection and twice on the day after the operation. The drains were removed on POD 3 if the bile concentration of the drain discharge was less than three times the serum bilirubin concentration on POD 3 and the amount of drain discharge on POD 3 was <500 ml (12). Intraoperative parameters, including blood loss, blood transfusion use, and the duration of surgery, were recorded.

Postoperative outcomes

Parameters associated with postoperative liver function (i.e., serum liver transferase and bilirubin levels) were measured on POD 1, 2, 3, 5, and 7. Postoperative complications were stratified according to the Clavien–Dindo classification (17). Major complications were defined as those of grade IIIa or higher. Bile leakage was defined according to the definitions of the International Study Group of Liver Surgery (ISGLS) (18). SSI was defined according to the Centers for Disease Control guidelines (19). Liver failure was diagnosed according to the ISGLS definition (20).

Statistical analyses

Continuous data are expressed as median and range values. Qualitative variables are expressed as frequencies (percentages). The t-test or Mann–Whitney *U* test was used for intergroup comparisons of quantitative variables, as appropriate, whereas the χ^2 test or Fisher's exact test was used to compare categorical data. Two-sided p-values of <0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS, Inc.).

Results

Baseline patient characteristics in the positive and negative drain culture groups

During the study period, a total of 195 consecutive patients underwent liver resection. There were 6 patients (3.1%) with positive drain cultures and 189 patients (96.9%) with negative drain cultures. Table 1 summarizes the characteristics of the patients with positive (the positive group) and negative drain cultures (the negative group). The proportion of patients with hepatocellular carcinoma was significantly higher in the negative group (16.7% vs. 49.7%), while the proportion of patients with colorectal liver metastasis was significantly higher in the positive group (50% vs. 29.1%). The positive group exhibited significantly higher alanine aminotransferase levels than the negative group (P=0.021). The proportions of patients who underwent major hepatectomy (P=0.026), bilioenteric anastomosis (P=0.011), and combined resection of the gastrointestinal tract (P<0.001) were significantly higher in the positive group.

Surgical outcomes in the positive and negative drain culture groups

Table 2 summarizes the surgical outcomes of the positive and negative groups. The duration of the operation and the amount of intraoperative blood loss did not differ significantly between the two groups. The positive group exhibited a significantly higher drain fluid bilirubin level on POD 3 than the negative group (2.5 vs. 2.0 mg/dL, P=0.031). The drainage period (6 vs. 3 days, P=0.01) and the duration of the postoperative hospitalization period (28.5 vs. 9 days, P=0.01) were significantly longer in the positive group. The incidence of liver failure was significantly higher in the positive group (33.3% vs. 12.7%, P=0.032). The incidence of SSI was significantly higher in the positive group (83.3% vs. 20.6%, P=0.002).

Multivariate analysis of risk factors for positive drain culture results

Table 3 shows the results of the multivariate analysis of the perioperative risk factors for positive drain culture results. Only the combined resection of the gastrointestinal tract (odds ratio: 24.4, P=0.006) was identified as an independent risk factor for positive drain culture results.

Univariate analysis of risk factors for surgical site infection

Table 4 shows the results of the univariate analysis of the perioperative risk factors for SSI. The proportion of patients who underwent major hepatectomy (P=0.011) was significantly higher in the with SSI group (P=0.011). The proportions of the duration of operation >300min and blood loss >1000g were significantly higher in the with SSI group (P=0.025, 0.042). The proportion of the drainage fluid bilirubin level on POD 1 >3mg/dL and positive drain culture was significantly higher in the with SSI group (P=0.001, 0.015).

Multivariate analysis of risk factors for surgical site infection

Table 5 shows the results of the multivariate analysis of the perioperative risk factors for SSI. The proportion of the drainage fluid bilirubin level on POD 1 >3mg/dL (odds ratio: 4.24, P=0.004) and positive drain culture (odds ratio: 8.04, P=0.035) were identified as independent risk factors for SSI.

Surgical outcomes of the patients in the positive and negative drain culture groups who did not undergo procedures involving the gastrointestinal tract

There were 182 patients who did not undergo bilioenteric anastomosis or combined resection of the gastrointestinal tract in this study. Two of these patients (1.1%) had positive drain culture results. Table 6 summarizes the surgical outcomes of the 182 patients. There were no significant differences in the frequencies of SSI between the two groups.

Bacteria in the drainage fluid of the patients that exhibited positive drain culture results on POD 1

There were 6 of 195 patients that exhibited positive drain culture results on POD 1. Four of the 6 patients had undergone procedures involving the gastrointestinal tract. The detected bacteria included *Corynebacterium* species, *Enterococcus* species, *Bacteroides distasonis,* coagulase-negative *Staphylococcus, Enterococcus faecium,* and methicillin-resistant *Staphylococcus aureus.*

Discussion

In this study, it was found that the detection of positive bacterial drainage fluid cultures on POD 1 and the drainage fluid bilirubin level on POD 1 >3mg/dL after liver resection associated with the development of SSI. On the other hand, combined resection of the gastrointestinal tract was identified as an independent risk factor for positive drain culture results on POD1. Positive bacterial cultures on POD1 were only detected in 1.1% (2/182) of the patients who did not undergo procedures involving the gastrointestinal tract, while 30.8% (4/13) of the patients with procedures involving the gastrointestinal tract were detected positive bacterial cultures on POD1. There have not been any studies about the relationship between the detection of positive bacterial drainage fluid culture results on POD 1 and postoperative complications after liver resection. Therefore, the present study might provide useful information about patient management after liver resection.

Bacterial cultures of drainage fluid have been used to investigate the outcomes of liver resection from the viewpoint of retrograde infections involving prophylactic drainage tubes. Tanaka et al. reported that the positivity rate of such cultures was significantly greater on POD 5 or later than on POD 4 or earlier (10). Yamazaki et al. reported that drain infections occurred between 2 and 16 days after surgery, and the median duration of drain infections was 7 days (11). Kyoden et al. examined the bacteria involved in such retrograde infections, and 36 of 57 (63.2%) cases involved normal skin flora (9). In the current study, normal skin flora was only detected in 1 case (16.7%). This might indicate that drain cultures performed on POD 1 are mainly affected by intestinal flora.

Migita et al. reported that the detection of positive drainage fluid culture results on POD 1 was an independent predictor of intra-abdominal abscess formation after gastrectomy (13). Sugiura et al. found that intraoperative bacterial contamination of the abdominal cavity has an adverse impact on the risk of SSI after pancreaticoduodenectomy (14). As the lumen of the gastrointestinal tract is usually exposed during gastrectomy or pancreaticoduodenectomy, enteric bacteria might be responsible for positive bacterial drainage fluid culture results and SSI after such procedures. On the other hand, liver resection itself does not require procedures involving the gastrointestinal tract. Actually, in this study 4 of 6 patients that exhibited positive culture results underwent bilioenteric anastomosis or resection for primary colorectal cancer. Another patient underwent cholecystectomy, and the remaining patient had previously undergone EST for choledocholithiasis. The existence of bacteria in bile might lead to positive drainage fluid culture results. If there were no bacteria present in bile, liver resection might be classified as a clean operation. In orthopedic surgery, which is classified as a clean form of surgery, the association between the results of bacterial cultures derived from drain tips that were removed on POD 1-2 and the development of SSI was studied, and in general it was indicated that there was no relationship between these factors (21-23).

In the present study, after excluding the patients who underwent procedures involving the gastrointestinal tract, it was found that positive drain culture results were not a predictor of SSI. On the other hand, the analysis of all patients indicated that positive drain culture results were significantly associated with SSI. In this study, 30.8% of patients who underwent procedures involving the gastrointestinal tract exhibited positive bacterial drainage fluid culture results on POD 1. It was reported that the SSI after simultaneous resection for synchronous colorectal liver metastasis was more frequently than liver resection only (24, 25). The results of the present study supported this reports. In cases in which procedures involving the gastrointestinal tract are performed in combination with liver resection, careful intraoperative management of the surgical field and intraoperative irrigation of the abdominal wall might be necessary.

This study had certain limitations. First, the study was retrospective in nature. Second, the sample size and the number of patients in which positive drain culture results were obtained were small. Despite these limitations, this study provides surgeons with valuable information regarding the culturing of drainage fluid during the early postoperative period after liver resection.

In conclusion, it was shown that the detection of positive bacterial drainage fluid culture results during the early postoperative period is significantly correlated with the development of SSI. However, the positive bacterial culture result was observed mainly after the liver resection concomitant with procedures involving the gastrointestinal tract, and not a predictor of SSI after liver resection without procedures involving the gastrointestinal tract.

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Table 1

Baseline patient characteristics in the positive and negative drain culture groups

	Positive group (n=6)	Negative group (n=189)	P
Age (year), median (range)	70.5 (49-77)	71 (34-85)	0.781
Gender, n (%)			0.185
Male	6 (100)	133 (70.4)	
Female	0 (0)	56 (29.6)	
Disease, n (%)			0.031
Hepatocellular carcinoma	1 (16.7)	94 (49.7)	
Colorectal liver metastasis	3 (50)	55 (29.1)	
Gallbladder carcinoma	2 (33.3)	10 (5.3)	
Other	0	30 (15.9)	
Prothrombin time, %, median (range)	86 (62-116)	93 (20-130)	0.331
Albumin, g/dL, median (range)	4.4 (3.6-5.2)	4.3 (2.8-5.3)	0.457
Serum bilirubin level, mg/dL, median (range)	0.9 (0.4-1)	0.7 (0.3-2.9)	0.772
Alanine aminotransferase level, U/L, median (range)	28 (7-131)	21 (7-114)	0.021
ICG-R15, %, median (range)	10.4 (3.8-17.9)	12.8 (0.5-56.2)	0.304
Child-Pugh classification, n (%)			1.000
A	6 (100)	186 (98.4)	
B	0 (0)	3 (1.6)	
Multiple tumors, n (%)	1 (16.7)	63 (33.3)	0.666
Repeat resection, n (%)	1 (16.7)	55 (29.1)	0.675
Anatomical resection, n (%)	3 (50)	94 (49.7)	1.000
Major hepatectomy, n (%)	3 (50)	21 (11.1)	0.026
Bilioenteric anastomosis, n (%)	2 (33.3)	4 (2.1)	0.011
Combined resection of the gastrointestinal tract, n (%)	3 (50)	5 (2.6)	<0.001
Cholecystectomy, n (%)	4 (66.7)	76 (40.2)	0.567
History of chemotherapy, n (%)	0	21 (11.1)	1.000
Diabetes, n (%)	2 (33.3)	48 (25.4)	0.647

Preoperative bile duct drainage, n (%)	0	2 (1.1)	1.000
Postoperative bile duct drainage, n (%)	0	3 (1.6)	1.000

ICG-R15: indocyanine green retention rate at 15 minutes

Table 2

Surgical outcomes in the positive and negative drain culture groups

	Positive group (n=6)	Negative group (n=189)	P
Duration of operation, min, median (range)	457 (227-870)	366 (100-981)	0.107
Duration of liver ischemia, min, median (range)	75 (0-200)	78 (0-311)	0.697
Blood loss, g, median (range)	425 (63-3735)	340 (0-9044)	0.313
Drainage fluid bilirubin level on POD 1, mg/dL, median (range)	1.0 (0.6-56.8)	1.2 (0.3-140.1)	0.320
Drainage fluid bilirubin level on POD 3, mg/dL, median (range)	2.5 (0.8-48.4)	2.0 (0.3-70)	0.031
Amount of drainage fluid on POD 1, mL, median (range)	290 (50-1250)	220 (5-1600)	0.137
Amount of drainage fluid on POD 3, mL, median (range)	200 (75-460)	67.5 (5-3280)	0.468
Duration of drainage period, days, median (range)	6 (1-56)	3 (1-114)	0.010
Clavien-Dindo classification (≥grade III), n (%)	2 (33.3)	29 (15.3)	0.243
Postoperative hospitalization period, days, median (range)	29 (8-64)	9 (5-162)	0.010
SSI, n (%)	5 (83.3)	35 (18.5)	0.002
Superficial/deep incisional, n (%)	2 (33.3)	10 (5.3)	0.005
Organ/space, n (%)	3 (50.0)	29 (15.3)	0.057
Bile leakage (ISGLS), n (%)	2 (33.3)	27 (14.3)	0.112
A	0	8 (4.2)	
B	1 (16.7)	15 (7.9)	
C	1 (16.7)	4 (2.1)	
Liver failure (ISGLS), n (%)	2 (33.3)	24 (12.7)	0.032
A	0 (0)	8 (4.2)	
B	1 (16.7)	16 (8.5)	

C	1 (16.7)	0 (0)	

POD: postoperative day, *SSI*: surgical site infection,

ISGLS: International Study Group of Liver Surgery

Table 3 Multivariate analysis of the risk factors for positive drain culture results

	Odds ratio	95% confidence interval	P-value
Disease	2.39	0.169-33.8	0.519
Bilioenteric anastomosis	15.9	0.5-507	0.117
Combined resection of the gastrointestinal tract	24.4	2.5-239	0.006
Alanine aminotransferase level	3.88	0.338-44.6	0.276
Major hepatectomy	0.984	0.0549-17.7	0.991

Table 4

Univariate analysis of perioperative risk factors for surgical site infection

	with SSI group (n=40)	without SSI group (n=155)	P
Age, >70, n (%)	23 (59.0)	80 (51.3)	0.474
Gender, Male, n (%)	27 (69.2)	112 (71.8)	0.843
Diabetes, n (%)	11 (28.2)	39 (25.0)	0.685
ICG-R15, >15%, n (%)	11 (28.2)	62 (39.7)	0.201
Child-Pugh classification, B, n (%)	1 (2.6)	2 (1.3)	0.49
Multiple tumors, n (%)	13 (33.3)	51 (32.7)	1
Repeat resection, n (%)	14 (35.9)	42 (26.9)	0.323
Anatomical resection, n (%)	21 (53.8)	76 (48.7)	0.595
Major hepatectomy, n (%)	10 (25.6)	14 (9.0)	0.011
Bilioenteric anastomosis, n (%)	3 (7.7)	3 (1.9)	0.096
Combined resection of gastrointestinal tract, n (%)	4 (10.3)	4 (2.6)	0.053
Cholecystectomy, n (%)	15 (38.5)	65 (41.7)	0.856
History of chemotherapy, n (%)	3 (7.7)	18 (11.5)	0.772
Duration of operation, >300min, n (%)	31 (79.5)	92 (59.0)	0.025
Duration of liver ischemia, >60min, n (%)	27 (69.2)	104 (66.7)	0.85
Blood loss, >1000g, n (%)	12 (30.8)	25 (16.0)	0.042
Drainage fluid bilirubin level on POD 1, >3mg/dL, n (%)	11 (28.2)	12 (7.7)	0.001
Amount of drainage fluid on POD 1, >500mL, n (%)	3 (7.7)	22 (14.1)	0.422
Positive drain culture, n (%)	4 (10.3)	2 (1.3)	0.015

ICG-R15: indocyanine green retention rate at 15 minutes *POD*: postoperative day, *SSI*: surgical site infection, *ISGLS*: International Study Group of Liver Surgery

Table 5

Multivariate analysis of perioperative risk factors for surgical site infection

	Odds ratio	95% confidence interval	P-value
Major hepatectomy	2.46	0.861-7.030	0.093
Duration of operation, ≧300min	2.11	0.844-5.270	0.110
Blood loss, ≧1000ml	1.12	0.428-2.950	0.813
Drainage fluid bilirubin level on POD 1, ≧3mg/dL	4.24	1.610-11.20	0.004
Positive drain culture	8.04	1.16-55.60	0.035

POD: postoperative day

Table 6

Surgical outcomes of the patients in the positive and negative drain culture groups who did not undergo procedures involving the gastrointestinal tract

	Positive group (n=2)	Negative group (n=180)	P
Duration of operation, min, median (range)	336 (242-430)	358 (100-936)	0.745
Duration of liver ischemia, min, median (range)	100 (0-200)	79 (0-311)	0.749
Blood loss, g, median (range)	108 (98-117)	336 (0-9044)	0.434
Drainage fluid bilirubin level on POD 1, mg/dl, median (range)	0.8 (0.6-1.0)	1.2 (0.3-140.1)	0.735
Amount of drainage fluid on POD 1, ml, median (range)	125 (100-150)	210 (10-1320)	0.363
Duration of drainage period, days, median (range)	13 (3-23)	3 (1-114)	0.495
Clavien-Dindo classification (≥grade III), n (%)	1 (50)	25 (13.9)	1.000
Postoperative hospitalization period, days, median (range)	17 (8-25)	8 (5-162)	0.797
SSI	1 (50)	28 (15.5)	0.294
Superficial/deep incisional SSI, n (%)	0	7 (3.9)	0.778
Organ/space SSI, n (%)	1 (50)	25 (13.9)	0.275
Bile leakage (ISGLS), n (%)			0.275
A	0	8 (4.4)	
B	1 (50)	13 (7.2)	
C	0	4 (2.2)	
Liver failure (ISGLS), n (%)			0.884
A	0	6 (3.3)	
B	0	14 (7.8)	
C	0	0	

POD: postoperative day, *SSI*: surgical site infection,

ISGLS: International Study Group of Liver Surgery