Original article

Clinicopathological parameters associated with surgical site infections in patients who underwent pancreatic resection

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Running title: Predictors of SSI in hepatectomy

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ABSTRACT

Background/Aims: To clarify parameters associated with postoperative surgical site infection (SSI) after pancreatectomy, we examined clinicopathological and surgical records in 186 patients who underwent pancreatectomy at a single academic institute.

Methodology: Patient demographics, liver functional parameters, histological findings, surgical records and post-hepatectomy outcomes during hospitalization were compared between the non-SSI and SSI group, in which SSIs included superficial and deep SSIs.

Results: The prevalence of SSI (29-35%) has not changed over an 18-year period. With respect to patient demographics and laboratory data, no parameters were associated with postoperative SSI. In surgical records, the operating time in the SSI group tended to be longer in comparison with that in the non-SSI group (618 vs. 553 minutes, respectively) but not significantly different ($p=0.070$). With respect to postoperative outcomes, time to oral intake in the SSI group was significantly longer than that in the non-SSI group (21.2 vs. 13.7 days, respectively) ($p<0.01$). Incidences of pancreatic fistula, postoperative bleeding, long-term ascites and re-operation were significantly more frequent in the SSI group in comparison with the non-SSI group ($p<0.05$). Decrease of body weight after surgery in the SSI group was significantly greater than that in the non-SSI group (-4.1 vs. -2.7kg, respectively) ($p<0.05$). Period of hospital stay in the SSI group was significantly longer than that in the non-SSI group (37 vs. 25 days) ($p<0.05$). Multivariate analysis showed that only postoperative pancreatic fistula was significantly associated with SSI ($p<0.01$).

Conclusions: SSI is an important risk factor of longer hospital stay after pancreatectomy and prevention of pancreatic fistula through the future improvement of surgical procedures is necessary to decrease SSI rates.

KEY WORDS: pancreatic resection; surgical site infection; patient outcome; pancreatic fistula

ABBREVIATIONS: Surgical site infection (SSI); International Study Group on Pancreatic Fistula Definition (ISGPF)

INTRODUCTION

Pancreatic resection is an invasive surgery leading to substantial blood loss, requiring red cell transfusion rate, physiological stress, and postoperative complications (e.g., pancreatic fistula and its related abscess formation or pseudoaneurysm). [1] Recently, perioperative management has been dramatically improved and surgical techniques using hemostatic devices or laparoscopic techniques have also been improved [1]. However, even with the improvement of pancreatic surgery, pancreatectomy-related surgical site infections (SSIs) are still a concern [2]. Organ SSIs in deep lesions are likely due to 1) fluid collection of pancreas juice or clots 2) medical instruments such as drainage tubes and staples, or 3) organ injury areas. Incisional SSIs in superficial lesions of the abdominal wall may be due to 1) exposure of digestive tract fluid or blood during operation or 2) bacteria flora usually located in the patient's skin. It is important to clarify the pancreatectomy-related parameters associated with SSIs within deep and superficial lesions, and it is necessary to take measures to avoid these SSI-associated factors. Several investigators have reported factors associated with SSI in patients who underwent pancreatectomy. [2-4]. In the present study, we aimed to further clarify these results by examining various clinicopathological and surgical parameters and determine changes over different time periods at a Japanese single cancer institute. Based on the present results, we propose measures to reduce the prevalence of SSIs.

In the present study, we examined perioperative clinicopathological parameters, experiences of surgeons, surgical records and postoperative morbidity and mortality in 186 patients with various pancreatic diseases who underwent pancreatectomy between 1994 and 2012. In 2004, the chief operator was changed although the first author continued to work as part of the same group for the entire period. We began to apply hemostatic vessel sealing devices in 2008. Therefore, the time periods were divided into three groups as group 1

(1994-2003), group 2 (2004-2007) and group 3 (2008-2012). Based on the results, we aimed to consider future strategies for SSI prevention during pancreatic surgery at our cancer institute.

METHODOLOGY

Patients

A total of 186 consecutive patients (124 men, 62 women) undergoing hepatic resection in the Division of Surgical Oncology and Department of Surgery at Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between 1994 and 2012 were analyzed. Mean and median age for patients at the time of surgery was 64.8 ± 12.3 and 66 years (range, 18-87 years). Subjects were divided by time periods: Term 1 had hepatectomy between 1994 and 2003 and included 54 patients (29%), term 2 was between 2000 and 2007 and included 99 patients (53%), and term 3 was between 2008 and 2012 and included 33 patients (18%). Background pancreas was normal in 115 patients (62%), and subacute pancreatitis was observed in 53 patients (29%), chronic pancreatitis in 9 (5%) and fatty pancreas in 7 (4%). Pancreas diseases were ampulla carcinoma in 21 patients (11%), bile duct carcinoma in 39 patients (21%), gallbladder carcinoma in five (3%), pancreatic ductal carcinoma in 60 (32%), duodenal tumors in four (2%), intraductal papillary mucin-producing neoplasm in 26 (14%), pancreatic neuroendocrine tumor in six (3%), chronic pancreatitis in nine (5%), and other benign liver diseases in 16 (9%). Diabetes mellitus was observed in 67 patients (36%), habit of smoking in 71 patients (38%), habit of alcohol every day in 82 (44%), co-existing pancreatitis in 51 (27%), and obesity (body mass index>25) in 36 (19%), respectively. The pancreatic functioning diagnostant (PFD) testing using N-benzoyl-l-tyrosyl-p-aminobenzoic acid was examined in 90 patients (48%). All study protocols were approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained from each patient during this period. Anesthetic and patient data were retrieved from the NUGSBS database.

Comparison of clinicopathological features, surgical records and postoperative outcomes.

Clinical data, co-morbidities, general status, conventional laboratory data, surgical data and pancreatectomy-related complications were analyzed. Evaluation of background pancreas and the main diseases were confirmed by histopathological examination of the resected specimen in all patients. We referred to the findings of the Classification of Pancreatic Carcinoma and Classification of Biliary Tract Carcinoma in biliary and pancreatic malignancies [5, 6]. The main operator was the teaching staff in 129 (69%) and fellowship or resident surgeon in 57 (31%). Operative procedures included pancreaticoduodenectomy (n=140; 75%), distal pancreatectomy (n=39; 21%) and central pancreatectomy (n=6; 3%) and Frey's pancreaticojejunostomy (n=1; 1%). All hepatic tumors were completely resected without macroscopic exposure of the amputated section to the remaining liver.

Statistical analysis

All continuous data are expressed as mean ±SD and median value. Differences were examined using one-way analysis of variance (ANOVA) and Student's t-test. Correlations between the two parameters were examined by calculating the Pearson's correlation coefficient. Categorical data were analyzed using Fisher's exact test. Potentially predictive variables were identified using a significance level of $p<0.05$ by univariate analysis and the identified factors were then entered into the multiple logistic regression analysis. A two-tailed value of $P<0.05$ was considered statistically significant. SPSS for Windows version 18.0 (SPSS, an IBM Company, Chicago, IL) was used for all statistical analyses.

RESULTS

Table 1 shows the prevalence of SSIs in the different periods. The prevalence of SSIs did not change significantly over the different periods examined from the past 18 years.

Table 2 shows the relationship between SSIs and demographics of patients who underwent pancreatectomy. Age, gender, background or main diseases of peripancreas lesions, habit, co-morbidity, general status and preoperative laboratory data were not significantly associated with occurrence of SSI.

Table 3 shows the surgical records. Operating time in the SSI group tended to be longer than that in the non-SSI group but this difference was not significant ($p=0.070$). Operators, incision, operating procedures, use of fibrin glue, blood loss, transfusion and architecture of pancreas were not significantly associated with occurrence of SSI.

Table 4 shows the patient outcomes. Time to oral intake after pancreatectomy in the SSI group was significantly longer than that in the non-SSI group ($p<0.01$). Incidences of pancreatic fistula, postoperative bleeding, long-term ascites, and reoperation in the SSI group were significantly more frequent in comparison with those in the non-SSI group ($p<0.05$). Decrease of body weight after pancreatectomy in the SSI group was significantly greater than that in the non-SSI group ($p<0.05$). Period of hospital stay in the SSI group was significantly longer than that in the non-SSI group ($p<0.05$).

Table 5 shows the risk ratio of parameters associated with SSI by multivariate analysis using the parameters. Only each grade of pancreatic fistula by the ISGPF classification was significantly associated with the occurrence of SSI ($p<0.01$).

DISCUSSION

Surgical site infection (SSI) is a major postoperative complication in pancreatic surgery and this complication may cause prolonged hospital stay. [2-4, 7-9]. Although SSI has been improved by the development of perioperative management, problematic issues remain. SSI is defined as infection in the superficial (incisional) and deep (organ space) sites [10]. In the present study, however, distinction of both SSI types was difficult using only patient charts and therefore we examined all cases of SSI together. As postoperative complications may improve over time [11], we firstly examined the changes of prevalence of SSI. However, the incidence of SSI was around 30% for all periods during the 18 years examined, with no improvement observed at our institute, even though we used absorbable materials and the latest vessel sealing devices. Previous reports showed the rate of SSI after pancreatectomy was higher than that in other gastrointestinal surgeries, which ranged between 20-40% [2, 3] The rate of SSI in the present study was within in a similar range. With respect to the prevention of postoperative infection, prophylactic antibiotics, such as the third-generation cephem antibiotics, administered by drip infusion were used for 7 days after pancreatectomy in the 1990s in our series. However, these prophylaxes might not be necessary because reliable evidence regarding effectiveness has not been fully elucidated. At the present stage, we have stopped such prophylactic treatment and the prevalence of SSI was not different. Shaving of pubic hair was previously performed to prevent incisional SSI at our institute; however, this procedure was also ceased in 2002 because no reliable evidence of its efficacy had been reported. Since 2004, silk sutures have been exchanged for absorbable materials to prevent SSI at our institute. When the abdominal wound is closed, we fully wash the intra-abdominal space using a large amount of saline to decrease the amount of remnant microorganisms. When the abdominal wall is closed, the incised wounds are again washed with a jet stream of saline.

The relationship between clinical and surgical features with SSI was examined. Although older age, diabetes, and co-morbidities present before surgery were previously reported to be associated with SSI [1-4, 7-9], in our study, no preoperative factors were significantly associated with SSI. Regarding diabetes, glycemic control was effective to prevent SSIs in patients undergoing pancreatectomy [12]. During the period of our study, strict management to control blood sugar after surgery was performed. Performance status might be associated with SSI in abdominal surgery. Patients with these parameters might have lower immunity according to worsening of systemic physiological functions. However, such a general status was not associated with SSI after pancreatectomy in the present study.

With respect to surgical records, in previous reports, patients who underwent laparoscopic operations showed low rates of SSI, likely because these operations are less invasive than laparotomy [1]. Gram-positive bacteria, such as a methicillin-resistance *Staphylococcus aureus*, were often detected on the surface wound [13]. However, the rate of SSI was not significantly decreased in patients undergoing laparoscopic pancreatectomy in comparison with conventional pancreatectomy in our study. Combined resections of surrounding vessels or intestinal anastomosis have also been proposed as risk factors of SSI; however, no significant relationship between SSI and these procedures was observed. Operating time tended to be significantly associated with SSI [14]. Longer exposure to air may increase the risk of attachment of microorganisms in the surgical field. Other surgical parameters, including blood loss, which was thought to be a risk factor [15], were not associated with the rate of SSI in the present study.

With respect to patient outcomes, SSIs frequently occurred when any postoperative complications were observed. Events of pancreatectomy-related complications might cause intra-abdominal infection due to deterioration of immunological defense mechanism as bacterial translocation or sepsis. Time to oral intake and body weight loss were also associated

with SSI in the present study. Such conditions might deteriorate nutritional status and immunological response, leading to SSI. On the other hand, this phenomenon might be a result of the occurrence of SSI or associated conditions [16]. Pancreatic fistula inducing enzyme activity of pancreas juice often causes intra-abdominal infection in the surgical space [17]. By multivariate analysis, the presence of pancreatic fistula was the most significant risk factor for SSI in the present study. Prevention of pancreatic fistula is necessary to reduce occurrence of SSI or hospital stay. However, the incidence of pancreatic fistula has not improved, even in the modern era, as previously reported [18]. More advanced surgical techniques to reduce pancreatic fistula in pancreatectomy are necessary in the future. Hospital-stay length was significantly affected by the high prevalence of post-pancreatectomy complications and deep SSI. SSI was thought to be an important factor affecting patient survival prognosis because this causes systemic sepsis and additional multi-organ dysfunction. Thus, occurrence of SSI is a risk factor for patient outcomes and prolonged hospital stay.

In conclusion, we have demonstrated the prevalence of SSI and we analyzed the relationship among SSI, surgical records and patient outcomes in patients with various diseases who underwent pancreatic resections. Prevalence of SSI did not change in the different time periods studied. Longer operating time, time to postoperative oral intake, postoperative complications and greater body weight loss were associated with SSI by univariate analysis and SSI was associated with longer hospital stay. Multivariate analysis showed that the presence of pancreas fistula and the degree of severity of pancreas fistula were independently associated with SSI. Preventing pancreatic fistula through advances in surgical procedures is important to reduce the prevalence of SSI and related patient outcomes.

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Table 1. Changes of prevalence of SSIs in different periods

	Term 1 (n=56)	Term 2 (n=78)	Term 3 (n=52)	Significance (p value)
Superficial SSI (n=32)	17(31%)	27(35%)	15(29%)	0.669

Table 2. Patient demographics, co-morbidities, general status and liver functional parameters in patients with or without SSI

	Non-SSI (n=127)	SSI (n=59)	Statistics (*p value*)
Age (years)	64.5±12.3	65.4±13.7	0.361
Gender			
Male/Female	82/45	42/17	0.472
Background chronic pancreatitis			
Normal/associated pancreatitis/ chronic pancreatitis/ fatty pancreas	78/39/6/3	37/15/3/4	0.478
Pancreas diseases			
Pancreatic cancer/ biliary cancer/ ampullar cancer/ NET/IPMN/others	47/24/16/5/17/18	13/20/5/3/10/8	0.172
Smoking			
No/ yes	79/48	36/23	1.0
Alcohol (drinking every day)			
No/ yes	73/54	30/29	0.491
Obesity (BMI>25)			
No/ yes	106/21	43/16	0.137
Diabetes			
No/ yes	82/45	38/21	1.0
Cardiovascular diseases			
No/ yes	115/12	52/7	0.805
Liver disease			
No/ yes	111/16	52/7	1.0
Renal diseases			
No/ yes	119/8	57/2	0.508
Performance status			
0/ 1	4/123	4/55	0.266
ASA physiological status[$]			
1/ 2/ 3	54/68/5	22/33/4	0.611
Laboratory data			

Hemoglobin (g/dl)	12.7±1.7	12.6±2.0	0.728
Creatinine (mg/dl)	0.9±0.8	1.0±0.3	0.822
Total protein (g/dl)	7.0±0.7	6.8±0.6	0.113
Albumin (g/dl)	4.0±0.5	3.9±0.5	0.181
Total bilirubin (mg/dl)	2.0±2.5	1.8±2.7	0.171
Amylase (U/l)	160±213	117±134	0.278
Total cholesterol (mg/dl)	184±65	181±50	0.533
Cholinesterase (mg/dl)	167±107	191±115	0.266
Blood sugar (mg/dl)	118±43	117±50	0.759

NET, neuroendocrine tumor; IPMN, intraductal papillary mucin producing neoplasm; BMI, body mass index; [$]American Society of Anesthesiologists

Table 3. Relationship between surgical records and SSI in patients undergoing pancreatectomy

	Non-SSI (n=127)	SSI (n=59)	Statistics (*p value*)
Operator			
Teaching staff/fellow/resident	80/42/5	40/14/5	0.240
Incision			
Laparoscopic/abdominal	10/117	1/58	0.177
Pancreatectomy			
PD/DP/Others	94/28/5	46/10/3	0.698
Combined resection of liver			
No/ yes	121/6	56/3	1.0
Pancreatojejunostomy			
No/ yes	14/113	5/54	0.784
Hardness of pancreas			
Soft/ hard	84/43	38/21	0.947
Node dissections			
None/D1/ D2 and 3	5/13/102	1/9/44	0.732
Tube drainage of the main pancreatic duct			
No/ lost tube/ external drainage	0/48/49	1/25/22	0.332
Use of fibrin glue			
No/ yes	25/102	13/46	0.862
Use of vessel sealer			
No/Yes	45/82	23/36	0.701
Operating time (minutes)	553±194	618±215	0.070
Blood loss (ml)	1323±959	1386±850	0.402
Red cell transfusion			
No/ yes	72/55	33/26	1.0
Use of fresh frozen plasma or albumin			
No/ yes	60/67	29/30	0.932
Advanced carcinoma (Stage III and IV)			
No/ yes	57/70	2435	0.704

Dilatation of main pancreatic duct			
<5mm/ ≥5mm	80/47	17/42	0.660

Table 4. Relationship between patient outcomes and SSI in patients undergoing hepatectomy

	Non-SSI (n=127)	SSI (n=59)	Statistics (*p value*)
Time to oral intake (days)	13.7±10.8	21.2±16.7	<0.01
Complications			
Pancreatic fistula			
No/grade A/ grade B and C*	117/8/2	25/22/12	<0.01
Postoperative bleeding			
No/yes	126/1	52/7	<0.01
Long-term ascites			
No/yes	116/11	47/12	0.044
Re-operation			
No/yes	125/2	52/7	<0.01
Decrease of body weight (kg)	-2.7±2.5	-4.1±3.5	0.028
Hospital stay (days)	25±18	37±29	0.012

*: Postoperative pancreatic fistula: an international study group (ISGPF) definition

Table 5. Relationship between associated parameters and superficial and deep SSI by multivariate logistic regression analysis

	SSI	
	OR (95% CI)	P value
Operating time		
≥510minutes vs. <510minutes	1.41 (0.61-3.24)	0.413
Time to oral intake		
≥13days vs. <12days	1.55 (0.67-3.59)	0.299
Decrease of body weight		
≥-3kg vs. <3kg	1.08 (0.38-3.07)	0.885
Pancreatic fistula*		
Grade A vs. no	6.84 (2.31-20.33)	<0.01
Grade BC vs. no	15.43 (2.68-88.75)	<0.01
Postoperative bleeding		
Yes vs. no	3.02 (0.24-38.63)	0.391
Long-term ascites		
Yes vs. no	2.48 (0.81-7.66)	0.110

Cut-off value was set at the median value of each continuous parameter

*: Postoperative pancreatic fistula: an international study group (ISGPF) definition