**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 51625

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Influence of bile contamination for patients who undergo pancreaticoduodenectomy after biliary drainage**

Okano K *et al.* Influence of bile contamination after pancreaticoduodenectomy

Keiichi Okano, Yasuyuki Suzuki

**Keiichi Okano, Yasuyuki Suzuki,** Departments of Gastroenterological Surgery, Kagawa University, Kita-gun, Kagawa 761-0793, Japan

**Author contributions**: Okano K and Suzuki Y designed and performed the research and wrote the paper.

**Corresponding author:** **Keiichi Okano, FACS, MD, PhD, Associate Professor,** Department of Gastroenterological Surgery, Kagawa University, 1750-1, Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan. kokano@med.kagawa-u.ac.jp

**Received:** September 29, 2019

**Revised:** December 7, 2019

**Accepted:** December 13, 2019

**Published online:** December 21, 2019

**Abstract**

BACKGROUND

The influence of bile contamination on the infectious complications of patients undergoing pancreaticoduodenectomy (PD) has not been thoroughly evaluated.

AIM

To evaluate the effect of preoperative biliary drainage and bile contamination on the outcomes of patients who undergo PD.

METHODS

The database of 4101 patients who underwent PD was reviewed. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

RESULTS

The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 50.8%) and bile contamination (34.3%, 26.2%, and 20.2%). Bile contamination was associated with postoperative pancreatic fistula (POPF) Grade B/C, wound infection, and catheter infection. A multivariate logistic regression analysis revealed that biliary contamination (odds ratio 1.33, *P* = 0.027) was the independent risk factor for POPF Grade B/C. The three most commonly cultured microorganisms from bile (*Enterococcus, Klebsiella, and Enterobacter)* were identical to those isolated from organ spaces.

CONCLUSION

In patients undergoing PD, bile contamination is related to postoperative infectious complication including POPF Grade B/C. The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.

**Key words:** Bile contamination; Complication; Pancreaticoduodenectomy; Preoperative biliary drainage; Postoperative pancreatic fistula Grade B/C

**Citation:** Okano K, Suzuki Y. Influence of bile contamination for patients who undergo pancreaticoduodenectomy after biliary drainage. *World J Gastroenterol* 2019; 25(47): 6847-6856

**URL:** https://www.wjgnet.com/1007-9327/full/v25/i47/6847.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v25.i47.6847

**Core tip**: This study aimed to evaluate the effect of preoperative biliary drainage and bile contamination on the outcomes of patients who undergo pancreaticoduodenectomy (PD). The database of 4101 patients who underwent PD was reviewed. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%). In patients undergoing PD, bile contamination is related to postoperative infectious complication including postoperative pancreatic fistula Grade B/C. The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.

**INTRODUCTION**

Pancreatoduodenectomy (PD) is a common and complex procedure in gastroenterological surgery. Although the perioperative mortality rate of PD in high-volume centres is reportedly 1% to 2%, the post-PD morbidity rate remains relatively high at 20% to 50%[[1-7](#_ENREF_1)]. In a previous study, we reported that infectious complications are the main cause of postoperative morbidity after PD[[8](#_ENREF_1)]. Nine risk factors for infectious complications after PD were identified: Male sex, age of 70 years or more, body mass index of at least 25 kg/m2, other previous malignancy, liver disease, bile contamination, surgery duration of 7 h or longer, intraoperative blood transfusion, and soft pancreas. Among these factors, bile contamination is the one that surgeons could control by appropriate perioperative management.

Obstructive jaundice is the most common symptom in patients with periampullary malignancy. Routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications[[9,10](#_ENREF_1)]. With the advent of neoadjuvant chemotherapy used to downstage potentially unresectable tumours in the hope of improving the outcome[[11,12](#_ENREF_1)], concern regarding preoperative biliary drainage during neoadjuvant treatment is clinically relevant. Preoperative endoscopic biliary procedures are widespread in the management of periampullary tumours[[13](#_ENREF_1)]. The effect of endoscopic procedures on biliary contamination and the immediate outcomes of PD remain controversial, although the several studies reported increased mortality or morbidity rate[[14-17](#_ENREF_1)]. This study aimed to identify the clinical features and outcomes after PD in patients with infected bile based on data from the Japanese Society of Pancreatic Surgery for future management of perioperative infectious complications.

**MATERIALS AND METHODS**

A nationwide multi-institutional analysis of infectious complications after major pancreatic surgery was conducted by the Japanese Society of Pancreatic Surgery. A database of 4101 patients who underwent PD during a 3-year period were analysed for this study. This study was approved by the Institutional Ethics Committee of Kagawa University.

***Definitions***

The definitions of complications including infectious complications are almost identical to those of the American College of Surgeons–National Surgical Quality Improvement Program criteria (NSQIP)[[18](#_ENREF_1)]. In the present study, infectious complications are defined as postoperative global infectious complications including surgical site infection [*i.e.*, wound infection, intra-abdominal abscess, infected postoperative pancreatic fistula (POPF)] and extraparieto-abdominal infection (*i.e.*, catheter infection, pneumonia, urinary tract infection). Infectious complications are also identified as a specific clinical condition that was related to infection by bacteria, fungus, or virus in a specific organ/compartment. A positive culture without correlation to a specific clinical condition was not considered an infectious complication.

As the NSQIP 30-d mortality rates underestimate the mortality rate for complicated surgical procedures such as PD[[7](#_ENREF_1)], the present study applied in-hospital mortality. In-hospital mortality was defined as death before postoperative day 30, and death among patients who were hospitalised for 30 d or more after surgery and died during that time[[7](#_ENREF_1)].

Complication severity was graded according to the Clavien–Dindo classification[[19](#_ENREF_1)]. Pancreatic fistula was defined according to the [International Study Group on Pancreatic Fistula](http://www.ncbi.nlm.nih.gov/pubmed?term=International%20Study%20Group%20on%20Pancreatic%20Fistula%20Definition%5BCorporate%20Author%5D) guidelines[[20](#_ENREF_1)] as an amylase level in the drainage fluid on postoperative day 3 that is > 3 times the normal serum amylase level. Grade A fistulas presented with elevated drain amylase levels only, and they lacked any clinical consequences. Grade B fistulas, requiring therapeutic interventions, behaved in an intermediate fashion, with marginal increases in duration of hospitalisation and rates of complications. Grade C fistulas were the most severe, and patients frequently required intensive care unit transfer for sepsis management. An infected pancreatic fistula was defined as a clinically relevant fistula with proven infection by positive culture. Postoperative intra-abdominal haemorrhage was defined as bleeding requiring a blood transfusion, reoperation, or interventional radiology. An intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures or organ/space surgical site infection in the abdominal cavity. A positive culture was not required to determine the presence of an infection, in cases in which NSQIP criteria were met and the clinical picture was consistent. Cultured organisms from organ space infections were determined by positive culture from the percutaneous drain, in patients with a clinical picture consistent with infection.

The types of biliary drainage and the results of preoperative bile culture were recorded for patients who underwent preoperative biliary drainage before PD. The preoperative biliary culture was performed in 1651 of 1964 patients (84.1%) who underwent biliary drainage in present study. Percutaneous trans-hepatic biliary drainage and endoscopic naso-biliary drainage were categorised as types of external drainage, and endoscopic retrograde biliary drainage was categorised as internal drainage. Positive results of cultured microorganisms in bile from a preoperative biliary stent or intraoperative bile collection were defined as bile contamination. Results of cultured microorganisms from overall infection site or organ space infections were collected from the patients with infectious complications. The standard perioperative management strategies were described previously[[8](#_ENREF_1)]. Drains were usually removed at 3 to 7 postoperative days according to the early removal policy.

***Statistical analysis***

All statistical analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC, United States). Patient characteristics and clinical factors were compared using the Mann-Whitney *U* test for continuous variables and Fisher’s exact test or the chi-squared test for categorical variables. Risk factors that were significantly associated with POPF Grade B/C in univariate models (*P* < 0.05) were included in a multivariate logistic regression model.Throughout this study, *P* values < 0.05 were considered statistically significant.

**RESULTS**

The median age of the 4101 patients included in this study was 68 years (range 6-89); 1920 patients (46.8%) were over 70 years old. The male to female ratio was 1.53:1. Preoperative biliary drainage was performed in 1964 of 4101 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

***Primary disease and infectious complications***

The primary disease was significantly associated with preoperative biliary drainage and bile contamination (Table 1). Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 5.80%) and bile contamination (34.3%, 26.2%, and 20.2%). In contrast, patients with intraductal papillary mucinous neoplasm, pancreas neuroendocrine tumour, and pancreas cystic tumour had a low frequency of preoperative biliary drainage and bile contamination at 10% or less.

***Background, outcomes, infectious complications, and cultured organisms***

There were significant differences in the age and sex ratio in patients with or without preoperative biliary drainage and bile contamination (Table 2). The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Preoperative biliary drainage was performed in male and elderly patients frequently. Bile contamination was also confirmed in male and elderly patients frequently. Preoperative biliary drainage and bile contamination were not associated with the rate of readmission and mortality. Bile contamination was associated with prolonged surgery duration. Preoperative biliary drainage and bile contamination were associated with both overall complications and infectious complications. Preoperative biliary drainage was associated with wound infection. Bile contamination was associated with POPF Grade B/C, wound infection, and catheter infection.

***Cultured organisms from the bile and organ space***

The most commonly cultured organisms from the bile were *Enterococcus* (42.7%), *Klebsiella* (26.6%), *Enterobacter* (14.2%), *Staphylococcus* (12.7%), and *E. Coli* (11.9%) (Table 3). The most commonly cultured organisms from the organ space (*n* = 596) were *Enterococcus* (47.7%), *Enterobacter* (20.0%), *Klebsiella* (14.8%), *Pseudomonas* (13.8%), and *Staphylococcus aureus* (methicillin-resistant *S. aureus*) (10.6%). These organisms were mainly cultured from drain discharge (*n* = 398) and intra-abdominal abscesses (*n* = 201 patients) which were strongly suspected to be associated with pancreatic fistula. The three most commonly cultured microorganisms from bile (*Enterococcus, Klebsiella, and Enterobacter)* were identical to those isolated from organ spaces. Most of the participating institutions (49 of 69 institutions) changed their antibiotic prophylaxis based on bile culture results in the present study.

***Risk factors influencing POPF Grade B/C***

Table 4 shows the results of multivariate analysis using risk factors that were significantly associated with POPF Grade B/C in univariate models. Six significant risk factors for infectious complications after PD were identified by multivariate analysis: male sex, age ≥ 70 years, body mass index ≥ 25 kg/m2, bile contamination, soft pancreas, and operative time ≥ 7 h. Preoperative biliary drainage was not independent significant risk factor.

The 1283 patients (40.5%) with high total bilirubin level (< 1.0g/dL) were compared with the 1886 patients (59.5%) with normal total bilirubin level (> 1.0g/dL) for incidence of all POPF and clinical relevant POPF (Grade B/C). There was no significant difference for all POPF (37.8% *vs* 39.5%, *P* = 0.55) or clinical relevant POPF (21.4% *vs* 20.6%, *P* = 0.82) between the patients with high and normal total bilirubin levels.

***Outcome according to the type of drainage***

Table 5 shows the demographic characteristics, perioperative variables, and immediate outcome according to the type of drainage (external or internal drainage) in 1942 patients who received PD. External drainage was performed in 772 patients (endoscopic nasobiliary drainage in 499 cases and percutaneous transhepatic biliary drainage in 273 cases) and internal drainage (endoscopic retrograde biliary drainage) was performed in 1170 patients. The duration of surgery was significantly longer in the patients with internal drainage than in those with external drainage. There were no significant differences between the two groups concerning the incidence of postoperative complications such as infectious complication, POPF, delayed gastric emptying, and intra-abdominal bleeding.

**DISCUSSION**

In this multicentre observational study, preoperative biliary drainage and bile contamination had a notable effect on the immediate outcomes after PD, with a high frequency of infectious complications. Especially, bile contamination had a strong association with POPF (Grade B/C). Bile contamination was present mainly in patients with pancreas cancer, bile duct carcinoma, and ampulla of Vater carcinoma. Furthermore, we found that the three most commonly cultured microorganisms from bile (*Enterococcus, Klebsiella, and Enterobacter)* were identical to those isolated from organ spaces. As the post-PD morbidity rate remains considerably high[[1-7](#_ENREF_1)], the prevention of bile contamination should be the most effective target to decrease the high morbidity after PD.

Several studies showed that early surgery without preoperative biliary drainage is the standard treatment in patients with resectable pancreatic head cancer presenting with jaundice[[9,10](#_ENREF_1)]. However, early surgery is not always feasible, and preoperative biliary drainage may be still necessary for patients with high hyper-bilirubinaemia at diagnosis or for those undergoing neoadjuvant treatment. It is still controversial how biliary drainage-related complications affect the incidence of postoperative complications after PD. Jagannath *et al*[[21](#_ENREF_1)] reported that a positive intraoperative bile culture was associated with higher morbidity rates after PD, and biliary drainage was not associated with increased morbidity. Cortes *et al*[[22](#_ENREF_1)] also reported that bile contamination had a remarkable effect on the immediate outcomes after PD for tumours, with a higher rate of infectious complications including wound and intraabdominal abscesses. Kitahata *et al*[[23](#_ENREF_1)] reported that patients undergoing internal drainage had a significantly higher incidence of cholangitis because of biliary drainage (22.4% *vs* 1.7% in the external drainage group). Internal drainage significantly increased the incidence of morbidity compared with external drainage (41.8% *vs* 22.3%). The present study analysed 772 and 1170 patients who received external and internal drainages, respectively, and no significant difference in postoperative complications was found between the internal and external drainage groups. The results suggested that the postoperative infectious complications for patients who underwent PD were not associated with type of biliary drainage.

The incidence of positive bile culture was reported to increase significantly in patients who underwent biliary drainage and presented complications such as cholangitis[[22](#_ENREF_1)]. Yanagimoto *et al*[[24](#_ENREF_1)] reported that preoperative cholangitis after biliary drainage was associated with development of POPF Grade B/C. The present study clearly revealed that significant association of bile contamination and POPF Grade B/C. The results strongly supported previous reports[[22,24](#_ENREF_1)]. Stent occlusion was reported to cause preoperative cholangitis, and cholangitis occurred in 26% of patients who underwent internal drainage[[9](#_ENREF_1)]. A possible mechanism to explain the association between cholangitis and internal drainage is the ascent of microorganisms from the open passage to the duodenum and subsequent reflux of duodenal contents[[25,26](#_ENREF_1)]. However, internal biliary drainage permits physiological bile flow, which is important for intestinal immunity and the prevention of bacterial translocation[[27-29](#_ENREF_1)]. Several studies reported that metalic stents have more advantages compared with plastic stents when used for preoperative biliary drainage in patients undergoing neoadjuvant therapy for pancreatic cancer[[30-32](#_ENREF_1)]. In two previous studies, stent-related complications were significantly higher with plastic stents than with fully covered self-expandable metal stents with no differences in the rate of overall surgical complications[[33,34](#_ENREF_1)]. Further studies are required to assess the fully covered self-expandable metal stents as preoperative biliary drainage affects the surgical procedure or perioperative outcome.

To our knowledge, this is the first report that clarified the specific causative microorganism profile for bile contamination in a large PD series. The *Enterococcus*, *Enterobacter*, and *Klebsiella* species were the more commonly cultured microorganisms from organ space infections and bile contamination. The illustration of different organisms is useful for selecting prophylactic antibiotics or considering drain management after pancreatic surgery. In addition, there were significant differences in the incidence of bile contamination among primary diseases. The results of cultured organisms suggest the need for tailored antibiotic prophylaxis for patients with a high risk of biliary contamination. In the present study, preoperative biliary culture was performed in 1651 of 1964 patients (84.1%) who underwent biliary drainage. Bile contamination was confirmed in 606 of 1651 patients (36.7%). Most of the participating institutions (49 of 69 institutions) changed their antibiotic prophylaxis based on bile culture results in the present study. As the specific antibiotic prophylaxis based on bile culture results prevents infectious complications in PD patients with preoperative biliary drainage[[35](#_ENREF_1)], preoperative bile culture should be considered in patients with biliary drainage. However, as there is currently no consensus regarding the appropriate type of antibiotic prophylaxis, a prospective study is warranted to provide evidence to validate appropriate antibiotic prophylaxis for patients with biliary contamination.

This multicentre study has several limitations. First, data were retrospectively collected, which makes it a potential source for significant bias. Second, the results may have been influenced by hospital volume, hospital training status, hospital compliance, and procedure-specific variables. Third, in some patients who received immediate internal drainage, a preoperative biliary culture was not obtained.Although these limitations are recognised, we believe that our findings will contribute to improving quality control in pancreatic surgery. Further prospective, randomised studies are needed to overcome these limitations.

In conclusion, preoperative biliary drainage and bile contamination had a notable effect on immediate outcomes after PD, with high frequency of infectious complications. Particularly, bile contamination is related to POPF Grade B/C. Management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both infected POPF and bile. These findings contribute to the proper management of patients with biliary drainage for PD and may help to establish perioperative therapeutic strategies for biliary contaminations.

**ARTICLE HIGHLIGHTS**

***Research background***

Preoperative endoscopic biliary procedures are widespread in the management of periampullary tumours. The influence of bile contamination on the infectious complications of patients undergoing pancreaticoduodenectomy (PD) has not been thoroughly evaluated.

***Research motivation***

The large data of clinical features and outcomes after PD in patients with infected bile will help improve future clinical outcome.

***Research objectives***

This study aimed to identify the clinical features and outcomes after PD in patients with infected bile based on data from the Japanese Society of Pancreatic Surgery for future management of perioperative infectious complications.

***Research methods***

We retrospectively reviewed the database of 4101 patients who underwent PD. Preoperative biliary drainage was performed in 1964 patients (47.9%), and bile contamination was confirmed in 606 patients (14.8%).

***Research results***

The incidence of postoperative infectious complications was 37.9% in patients with preoperative biliary drainage and 42.4% in patients with biliary contamination, respectively. Patients with extrahepatic bile duct carcinoma, ampulla of Vater carcinoma, and pancreatic carcinoma had a high frequency of preoperative biliary drainage (82.9%, 54.6%, and 50.8%) and bile contamination (34.3%, 26.2%, and 20.2%). Bile contamination was associated with postoperative pancreatic fistula (POPF) Grade B/C, wound infection, and catheter infection. A multivariate logistic regression analysis revealed that biliary contamination (odds ratio 1.33, *P* = 0.027) was the independent risk factor for POPF Grade B/C. The three most commonly cultured microorganisms from bile (*Enterococcus, Klebsiella, and Enterobacter)* were identical to those isolated from organ spaces.

***Research conclusions***

In patients undergoing PD, bile contamination is related to postoperative infectious complication including POPF Grade B/C.

***Research perspectives***

The management of biliary contamination should be standardised for patients who require preoperative biliary drainage for PD, as the main microorganisms are identical in both organ spaces and bile.

**REFERENCES**

1 **Winter JM**, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006; **10**: 1199-210; discussion 1210-1 [PMID: 17114007 DOI: 10.1016/j.gassur.2006.08.018]

2 **Cameron JL**, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006; **244**: 10-15 [PMID: 16794383 DOI: 10.1097/01.sla.0000217673.04165.ea]

3 **Vin Y**, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF, Allen PJ. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. *J Am Coll Surg* 2008; **207**: 490-498 [PMID: 18926450 DOI: 10.1016/j.jamcollsurg.2008.05.003]

4 **Yeo CJ**, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248-57; discussion 257-60 [PMID: 9339931 DOI: 10.1097/00000658-199709000-00004]

5 **Buchler MW,** Friess H, Muller MW, Wheatley AM, Beger HG. Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis. American journal of surgery 1995;169(1): 65-69; discussion 69-70 [DOI: 10.1016/S0002-9610(99)80111-1]

6 **Simons JP**, Shah SA, Ng SC, Whalen GF, Tseng JF. National complication rates after pancreatectomy: beyond mere mortality. *J Gastrointest Surg* 2009; **13**: 1798-1805 [PMID: 19506975 DOI: 10.1007/s11605-009-0936-1]

7 **Kimura W**, Miyata H, Gotoh M, Hirai I, Kenjo A, Kitagawa Y, Shimada M, Baba H, Tomita N, Nakagoe T, Sugihara K, Mori M. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. *Ann Surg* 2014; **259**: 773-780 [PMID: 24253151 DOI: 10.1097/SLA.0000000000000263]

8 **Okano K**, Hirao T, Unno M, Fujii T, Yoshitomi H, Suzuki S, Satoi S, Takahashi S, Kainuma O, Suzuki Y. Postoperative infectious complications after pancreatic resection. *Br J Surg* 2015; **102**: 1551-1560 [PMID: 26387569 DOI: 10.1002/bjs.9919]

9 **van der Gaag NA**, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]

10 **Fang Y**, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. *Br J Surg* 2013; **100**: 1589-1596 [PMID: 24264780 DOI: 10.1002/bjs.9260]

11 **Winner M**, Goff SL, Chabot JA. Neoadjuvant therapy for non-metastatic pancreatic ductal adenocarcinoma. *Semin Oncol* 2015; **42**: 86-97 [PMID: 25726054 DOI: 10.1053/j.seminoncol.2014.12.008]

12 **Li D**, O'Reilly EM. Adjuvant and neoadjuvant systemic therapy for pancreas adenocarcinoma. *Semin Oncol* 2015; **42**: 134-143 [PMID: 25726058 DOI: 10.1053/j.seminoncol.2014.12.012]

13 **Umeda J**, Itoi T. Current status of preoperative biliary drainage. *J Gastroenterol* 2015; **50**: 940-954 [PMID: 26138070 DOI: 10.1007/s00535-015-1096-6]

14 **Povoski SP**, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. *Ann Surg* 1999; **230**: 131-142 [PMID: 10450725 DOI: 10.1097/00000658-199908000-00001]

15 **Sohn TA,** Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg 2000;4(3): 258-267; discussion 267-258 [DOI: 10.1016/S1091-255X(00)80074-8]

16 **Pisters PW**, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S, Raijman I, Evans DB. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001; **234**: 47-55 [PMID: 11420482 DOI: 10.1097/00000658-200107000-00008]

17 **Srivastava S**, Sikora SS, Kumar A, Saxena R, Kapoor VK. Outcome following pancreaticoduodenectomy in patients undergoing preoperative biliary drainage. *Dig Surg* 2001; **18**: 381-387 [PMID: 11721113 DOI: 10.1159/000050178]

18 **American College of Surgeons**. User Guide for the 2012 Participant Use Data File. American College of Surgeons National Surgical Quality Improvement Program 2012. Available from: https://accreditation.facs.org/Programs/PreApp

19 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

20 **Bassi C**, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8-13 [PMID: 16003309 DOI: 10.1016/j.surg.2005.05.001]

21 **Jagannath P**, Dhir V, Shrikhande S, Shah RC, Mullerpatan P, Mohandas KM. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. *Br J Surg* 2005; **92**: 356-361 [PMID: 15672425 DOI: 10.1002/bjs.4864]

22 **Cortes A**, Sauvanet A, Bert F, Janny S, Sockeel P, Kianmanesh R, Ponsot P, Ruszniewski P, Belghiti J. Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. *J Am Coll Surg* 2006; **202**: 93-99 [PMID: 16377502 DOI: 10.1016/j.jamcollsurg.2005.09.006]

23 **Kitahata Y**, Kawai M, Tani M, Hirono S, Okada K, Miyazawa M, Shimizu A, Yamaue H. Preoperative cholangitis during biliary drainage increases the incidence of postoperative severe complications after pancreaticoduodenectomy. *Am J Surg* 2014; **208**: 1-10 [PMID: 24530042 DOI: 10.1016/j.amjsurg.2013.10.021]

24 **Yanagimoto H**, Satoi S, Yamamoto T, Toyokawa H, Hirooka S, Yui R, Yamaki S, Ryota H, Inoue K, Michiura T, Matsui Y, Kwon AH. Clinical impact of preoperative cholangitis after biliary drainage in patients who undergo pancreaticoduodenectomy on postoperative pancreatic fistula. *Am Surg* 2014; **80**: 36-42 [PMID: 24401513]

25 **Hochwald SN**, Burke EC, Jarnagin WR, Fong Y, Blumgart LH. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch Surg* 1999; **134**: 261-266 [PMID: 10088565 DOI: 10.1001/archsurg.134.3.261]

26 **Lermite E**, Pessaux P, Teyssedou C, Etienne S, Brehant O, Arnaud JP. Effect of preoperative endoscopic biliary drainage on infectious morbidity after pancreatoduodenectomy: a case-control study. *Am J Surg* 2008; **195**: 442-446 [PMID: 18304506 DOI: 10.1016/j.amjsurg.2007.03.016]

27 **Clements WD**, Diamond T, McCrory DC, Rowlands BJ. Biliary drainage in obstructive jaundice: experimental and clinical aspects. *Br J Surg* 1993; **80**: 834-842 [PMID: 7690298 DOI: 10.1002/bjs.1800800707]

28 **Parks RW**, Clements WD, Smye MG, Pope C, Rowlands BJ, Diamond T. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. *Br J Surg* 1996; **83**: 1345-1349 [PMID: 8944448 DOI: 10.1002/bjs.1800831007]

29 **Kamiya S**, Nagino M, Kanazawa H, Komatsu S, Mayumi T, Takagi K, Asahara T, Nomoto K, Tanaka R, Nimura Y. The value of bile replacement during external biliary drainage: an analysis of intestinal permeability, integrity, and microflora. *Ann Surg* 2004; **239**: 510-517 [PMID: 15024312 DOI: 10.1097/01.sla.0000118594.23874.89]

30 **Tol JA**, van Hooft JE, Timmer R, Kubben FJ, van der Harst E, de Hingh IH, Vleggaar FP, Molenaar IQ, Keulemans YC, Boerma D, Bruno MJ, Schoon EJ, van der Gaag NA, Besselink MG, Fockens P, van Gulik TM, Rauws EA, Busch OR, Gouma DJ. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. *Gut* 2016; **65**: 1981-1987 [PMID: 26306760 DOI: 10.1136/gutjnl-2014-308762]

31 **Aadam AA**, Evans DB, Khan A, Oh Y, Dua K. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. *Gastrointest Endosc* 2012; **76**: 67-75 [PMID: 22483859 DOI: 10.1016/j.gie.2012.02.041]

32 **Crippa S**, Cirocchi R, Partelli S, Petrone MC, Muffatti F, Renzi C, Falconi M, Arcidiacono PG. Systematic review and meta-analysis of metal versus plastic stents for preoperative biliary drainage in resectable periampullary or pancreatic head tumors. *Eur J Surg Oncol* 2016; **42**: 1278-1285 [PMID: 27296728 DOI: 10.1016/j.ejso.2016.05.001]

33 **Kahaleh M,** Tokar J, Conaway MR, Brock A, Le T, Adams RB, Yeaton P. Efficacy and complications of covered Wallstents in malignant distal biliary obstruction. Gastrointestinal endoscopy 2005; 61: 528-533 [DOI: 10.1016/S0016-5107(04)02593-3]

34 **Soderlund C**, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2006; **63**: 986-995 [PMID: 16733114 DOI: 10.1016/j.gie.2005.11.052]

35 **Sudo T**, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Ohge H, Sueda T. Specific antibiotic prophylaxis based on bile cultures is required to prevent postoperative infectious complications in pancreatoduodenectomy patients who have undergone preoperative biliary drainage. *World J Surg* 2007; **31**: 2230-2235 [PMID: 17726628 DOI: 10.1007/s00268-007-9210-4]

**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of the Kagawa University Hospital

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** No additional data are available

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited Manuscript

**Peer-review started:** September 29, 2019

**First decision:** November 27, 2019

**Article in press:** December 13, 2019

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Japan

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Yu XJ, Zhang XF **S-Editor:** Wang J **L-Editor:** A **E-Editor:** Ma YJ

**Figure Legends**

**Table 1 Primary disease and bile contamination in patients who received pancreaticoduodenectomy, *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Preoperative biliary drainage** | | ***P* value** | **Bile contamination** | | ***P* value** |
| **Yes (*n* = 1964)** | **No (*n* = 2137)** | **Yes *(n* = 606)** | **No (*n* = 2130)** |
|
| Disease |  |  | < 0.0001 |  |  | < 0.0001 |
| Pancreatic cancer | 955 (50.8) | 925 (49.2) |  | 261 (20.2) | 1029 (79.8) |  |
| Bile duct carcinoma | 691 (82.9) | 143 (17.1) |  | 208 (34.3) | 399 (65.7) |  |
| Intraductal papillary mucinous Neoplasm | 19 (4.5) | 406 (95.5) |  | 10 (5.1) | 187 (94.9) |  |
| Ampulla of Vater carcinoma | 250 (54.6) | 208 (45.4) |  | 78 (26.2) | 220 (73.8) |  |
| Pancreas neuroendocrine tumour | 11 (8.9) | 113 (91.1) |  | 3 (4.2) | 69 (95.8) |  |
| Pancreas cystic tumour | 3 (2.6) | 113 (97.4) |  | 1 (2.9) | 34 (97.1) |  |
| Duodenal cancer | 23 (18.3) | 103 (81.7) |  | 7 (9.7) | 65 (90.3) |  |

**Table 2 Association of preoperative biliary drainage and bile contamination with immediate outcome after pancreaticoduodenectomy, *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Preoperative biliary drainage** | | ***P* value** | **Bile contamination** | | ***P* value** |
| **Yes (*n* = 1964)** | **No (*n* = 2137)** | **Yes (*n* = 606)** | **No (*n* = 2130)** |
| Demographics | | | | | | |
| Age (yr), median | 69 | 68 | < 0.0001 | 69 | 68 | 0.0004 |
| Sex ratio (M:F) | 1.81:1 | 1.34:1 | < 0.0001 | 2.11:1 | 1.56:1 | 0.0012 |
| Duration of hospital stay (d), median | 29 | 29 | 0.29 | 29 | 31 | 0.11 |
| Readmission | 64 (3.3) | 84 (3.9) | 0.25 | 19 (3.1) | 91 (4.3) | 0.33 |
| In-hospital death | 42 (2.1) | 34 (1.6) | 0.21 | 8 (1.3) | 46 (2.2) | 0.19 |
| Operative variables | | | | | | |
| Estimated blood loss (g), median | 855 | 643 | < 0.0001 | 875 | 759 | 0.053 |
| Duration of surgery (min), median | 487 | 461 | < 0.0001 | 497 | 483 | 0.0005 |
| Postoperative complications | | | | | | |
| Overall complications | 1084 (55.2) | 1114 (52.1) | 0.049 | 356 (58.7) | 1130 (53.1) | 0.0014 |
| Infectious complications | 744 (37.9) | 714 (33.4) | 0.003 | 257 (42.4) | 746 (35.0) | 0.0003 |
| Severe complications (grade III or more) | 340 (17.3) | 316 (14.8) | 0.036 | 110 (18.2) | 321 (15.0) | 0.039 |
| POPF (all) | 739 (37.6) | 809 (37.9) | 0.42 | 246 (40.6) | 773 (36.3) | 0.06 |
| Delayed gastric emptying | 111 (5.7) | 144 (6.7) | 0.18 | 40 (6.6) | 143 (6.7) | 0.42 |
| Intra-abdominal bleeding | 67 (3.4) | 57 (2.7) | 0.16 | 18 (3.0) | 61 (2.9) | 0.78 |
| Details of infectious complication | | | | | | |
| POPF (ISGPF Grade B or C) | 444 (22.6) | 438 (20.5) | 0.13 | 154 (25.4) | 432 (20.3) | 0.003 |
| Wound infection | 320 (16.3) | 216 (10.3) | < 0.0001 | 93 (15.3) | 263 (12.3) | 0.045 |
| Intra-abdominal abscess | 289 (14.7) | 295 (14.0) | 0.53 | 94 (15.5) | 293 (13.8) | 0.23 |
| Cholangitis | 79 (4.1) | 95 (4.5) | 0.45 | 24 (4.0) | 105 (4.9) | 0.35 |
| Pneumonia | 61 (3.1) | 61 (2.9) | 0.7 | 21 (3.5) | 66 (3.1) | 0.62 |
| Liver abscess | 21 (1.1) | 24 (1.2) | 0.83 | 9 (1.5) | 19 (0.9) | 0.21 |
| Sepsis | 86 (4.5) | 86 (4.2) | 0.66 | 30 (5.0) | 83 (3.9) | 0.24 |
| Pseudomembranous enteritis | 31 (1.6) | 30 (1.4) | 0.68 | 13 (2.1) | 27 (1.3) | 0.12 |
| Catheter infection | 91 (4.7) | 115 (5.5) | 0.24 | 41 (6.8) | 98 (4.6) | 0.029 |
| Fungaemia | 28 (1.5) | 28 (1.4) | 0.8 | 8 (1.3) | 25 (1.2) | 0.75 |

The variables were identical to those of the American College of Surgeons–National Surgical Quality Improvement Program.POPF: Postoperative pancreatic fistula; ISGPF: Influencing postoperative pancreatic fistula.

**Table 3 Comparison of cultured organisms from bile and organ space infections**

|  |  |
| --- | --- |
| **Characteristic** | ***n* (%)** |
| Cultured from bile | 606 |
| *Enterococcus* | 259 (42.7) |
| *Klebsiella* | 161 (26.6) |
| *Enterobacter* | 86 (14.2) |
| *Streptococcus* | 77 (12.7) |
| *E.coli* | 72 (11.9) |
| *Other Gram negative rods* | 59 (9.7) |
| *Citrobacter* | 42 (6.9) |
| *Pseudomona* | 38 (6.3) |
| *Coagulase negative staphyloccoccus* | 34 (5.6) |
| *Candida albicans* | 23 (3.8) |
| *Staphylococcus aureus (MRSA)* | 20 (3.3) |
| *Staphylococcus aureus (MSSA)* | 10 (1.7) |
| Cultured from organ space | 596 |
| *Enterococcus* | 284 (47.7) |
| *Enterobacter* | 119 (20.0) |
| *Klebsiella* | 88 (14.8) |
| *Pseudomona* | 82 (13.8) |
| *Staphylococcus aureus (MRSA)* | 63 (10.6) |
| *Candida albicans* | 58 (9.7) |
| *Coagulase-negative Staphylococcus* | 55 (9.2) |
| *Streptococcus* | 51 (8.6) |
| *Staphylococcus aureus (MSSA)* | 48 (8.1) |
| *E.coli* | 26 (4.4) |

MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-sensitive *S. aureus*.

**Table 4 Multivariate analysis for risk factors influencing postoperative pancreatic fistula (Grade B/C) patients who received pancreaticoduodenectomy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk factor** | **Significance (*P* value)** | **Odds ratio** | **95%CI** |
| Male sex | < 0.0001 | 1.815 | 1.459-2.266 |
| Age ≥ 70 | 0.032 | 1.250 | 1.018-1.535 |
| BMI (kg/m2) ≥ 25 | < 0.0001 | 2.095 | 1.610-2.718 |
| Other previous malignancies | 0.079 | 1.253 | 0.971-1.612 |
| Liver disease | 0.119 | 1.422 | 0.903-2.200 |
| Preoperative biliary drainage | 0.461 | 1.087 | 0.869-1.361 |
| Bile contamination | 0.026 | 1.338 | 1.033-1.729 |
| Soft pancreas | < 0.0001 | 4.594 | 3.650-5.824 |
| Operation time (h) ≥ 7 | 0.0021 | 1.441 | 1.143-1.822 |

BMI: Body mass index; NA: Not available; POPF: Postoperative pancreatic fistula; ISGPF: International Study Group on Pancreatic Fistula; CI: Confidence interval.

**Table 5 Comparison of complications and immediate outcome according to the type of drainage (external or internal) after pancreaticoduodenectomy, *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Type of biliary drainage** | | ***P* value** |
| **External (*n* = 772)** | **Internal (*n* = 1170)** |
| Demographics | | | |
| Age (yr), median | 64 | 62 | 0.025 |
| Sex ratio (M:F) | 1.97:1 | 1.84:1 | 0.99 |
| Duration of hospital stay (d), median | 30 | 28 | 0.72 |
| Readmission | 29 (3.8) | 36 (3.1) | 0.32 |
| In-hospital death | 15 (1.9) | 27 (2.3) | 0.58 |
| Operative variables | | | |
| Estimated blood loss (g), median | 855 | 860 | 0.75 |
| Duration of surgery (min), median | 475 | 500 | 0.0004 |
| Postoperative complications | | | |
| Overall complications | 433 (56.1) | 646 (55.2) | 0.7 |
| Infectious complications | 293 (38.0) | 445 (38.0) | 0.77 |
| Severe complications (grade III or more) | 127 (16.5) | 211 (18.0) | 0.35 |
| POPF (all) | 284 (36.8) | 450 (38.5) | 0.57 |
| POPF (ISGPF Grade B or C) | 164 (21.2) | 277 (19.4) | 0.19 |
| Delayed gastric emptying | 97 (12.6) | 166 (14.2) | 0.37 |
| Intra-abdominal bleeding | 36 (4.7) | 68 (5.8) | 0.32 |

The variables were identical to those of the American College of Surgeons–National Surgical Quality Improvement Program. Percutaneous transhepatic biliary drainage and endoscopic nasobiliary drainage were categorized as the types of external drainage and endoscopic retrograde biliary drainage was categorized as internal drainage. External drainage was performed in 772 patients (endoscopic nasobiliary drainage in 499 cases, percutaneous transhepatic biliary drainage in 241 cases, and PTGBD in 32 cases) and internal drainage was performed in 1170 patients.POPF: Postoperative pancreatic fistula.