Q1. Conspicuous case history. Topic debated in literature. Some aspects should be better specified by the authors. Do all patients undergo preoperative biliary drainage?

ANS: Thank you for your inquiry. In this retrospective study, spanning 689 cases of pancreaticoduodenectomy conducted at our institute, 416 cases underwent surgery directly without preoperative biliary drainage. The inclusion criteria for our study encompassed patients who had undergone preoperative biliary drainage before undergoing therapeutic pancreaticoduodenectomy for malignancies or suspected malignancies affecting the pancreatic or periampullary regions. Conversely, patients who had not undergone preoperative biliary drainage preceding pancreaticoduodenectomy were excluded from the study at the beginning.

Q2. Do patients undergo drainage with any level of hyperbilirubinemia?

ANS: Thank you for your inquiry. Patients who underwent biliary drainage due to obstructive jaundice typically presented with a certain level of hyperbilirubinemia, ranging from a median total bilirubin level of 10-14 mg/dL, and this is the consensus of the MDT (multidisciplinary team) in our institute. However, ERCP may be arranged under some consideration, such as the presentation of biliary tract infection and the possibility of diagnosis, for which surgery may not be the first consideration. In the past 1 to 2 years, patients with suspicious pancreatic cancer (resectable disease) may have ERCP due to the consideration of neoadjuvant chemotherapy in our institute.

Q3. How many days after bile drainage is surgical treatment performed?

ANS: Thank you for your inquiry. The timing of surgical intervention was predicated upon individual clinical assessments conducted by the surgeon. Typically, this

intervention occurred within a timeframe ranging from 7 to 21 days following biliary drainage in our cohort. The variance in timing was contingent upon several factors. Firstly, if complications arise from biliary drainages, such as pancreatitis, hemorrhaging, or infection, priority was given to stabilizing the patient before surgery. Secondly, in cases where patients underwent ERCP biopsy concurrent with drainage, surgery was not arranged until the biopsy results were issued. The details of the timing of the surgery were discussed in the section: "***Material and methods: 2.2 Preoperative biliary interventions (PBI) and surgical procedures***".

Q4. How many patients have undergone neoadjuvant treatments?

ANS: Thank you for your inquiry. None of the patients in our study population underwent neoadjuvant chemoradiotherapy. The data for our research spanned from June 2013 to March 2022. Neoadjuvant treatment and conversion surgery were not implemented in our institute until 2022, and the population eligible for such treatments was notably small. Those who did receive neoadjuvant chemoradiotherapy in our institute typically had borderline resectable pancreatic cancer or clinical lymph node-positive patients.

Q5. Have any differences been noted between patients with cephalopancreatic carcinoma and patients with carcinoma in other periampullary locations?

ANS: In the univariate analysis, females exhibited a higher prevalence in pancreatic cancer cases compared to males (46.6% vs. 33.8%, P=0.04). Additionally, levels of preoperative total bilirubin and ALT were elevated in patients diagnosed with cephalopancreatic cancer, with mean levels of 4.4 mg/dL and 122.9 U/L, respectively.

In contrast, patients with periampullary cancer demonstrated lower mean total bilirubin levels of 2.6 mg/dL and ALT levels of 71.3 U/L, with corresponding P values of 0.002 and <0.001, respectively. The rates of preoperative biliary tract infection and positive intraoperative bile culture were significantly higher in patients with other cancers compared to pancreatic cancer.

Upon multivariate analysis, no significant differences were observed in patient stratification or other outcome comparisons regarding postoperative biliary tract infection, BTI-related septic shock, and mortality. However, the positive yield of intraoperative biliary culture was higher in patients with carcinoma located in other periampullary regions than those with pancreatic cancer (73.6% vs. 43.6%, P= 0.009). Also, the rate of preoperative biliary tract infection was also higher in the non-pancreatic cancer group (35.1% vs. 22.9, P=0.023)

While our study primarily focused on assessing the impact of preoperative biliary drainage, the observed variations among different types of cancer are noteworthy. Following is the table comparing pancreatic cancer and other cancers.

comparison between pancreatic CA and other Cas						
		Overall	**Pancreatic CA**	**others**	**Univariate analysis**	**Multivariate analysis**
n		279	131	148		
Age, mean (SD)		65.0 (11.5)	65.3 (10.8)	64.8 (12.1)	0.717	NA
Sex, n (%)	**Female**	111 (39.8)	61 (46.6)	50 (33.8)	0.040*	0.64
	Male	168 (60.2)	70 (53.4)	98 (66.2)		NA
ASA≥3, n (%)	**yes**	130 (46.6)	64 (48.9)	66 (44.6)	0.554	NA
WBC, mean (SD)		7.7 (2.9)	7.5 (3.1)	7.8 (2.8)	0.328	NA
Hb, mean (SD)		11.7 (2.0)	11.8 (2.1)	11.6 (2.0)	0.448	NA

PLT, mean (SD)		284.0 (98.2)	289.0 (100.1)	280.1 (96.9)	0.485	NA
TB, mean (SD)		3.4 (4.5)	4.4 (5.3)	2.6 (3.5)	0.002*	NA
AST, mean (SD)		72.2 (83.0)	86.5 (107.7)	60.8 (54.1)	0.026*	NA
ALT, mean (SD)		94.1 (102.6)	122.9 (131.3)	71.3 (64.2)	<0.001*	NA
ALKP, mean (SD)		235.4 (187.4)	251.8 (207.8)	222.2 (168.8)	0.255	NA
Albumin, mean (SD)		4.4 (10.6)	3.7 (0.5)	4.9 (14.1)	0.356	0.180
CA199, mean (SD)		933.8 (3745.5)	1000.7 (3894.7)	880.0 (3635.3)	0.807	NA
CEA, mean (SD)		12.2 (87.1)	23.8 (130.5)	3.1 (5.7)	0.108	NA
Pre OP BTI, n (%)	**yes**	82 (29.4)	30 (22.9)	52 (35.1)	0.035*	0.023*
Surgery type, n (%)	**PD**	191 (68.5)	98 (74.8)	93 (62.8)	0.044	0.781
Bile culture, n (%)	**Positive**	170 (60.9)	61 (46.6)	109 (73.6)	<0.001*	0.009*
Post op BTI, n (%)	**yes**	27 (9.7)	12 (9.2)	15 (10.1)	0.943	NA
complication≥3, n (%)	**yes**	23 (8.2)	7 (5.3)	16 (10.8)	0.150	0.999
BTI-related septic shock, n (%)	**yes**	5 (1.8)	2 (1.5)	3 (2.0)	1.000	NA
Mortality, n (%)	**yes**	4 (1.4)	1 (0.8)	3 (2.0)	0.625	NA