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Original research

Comparison of prognosis between patients of pancreatic head cancer with and without obstructive jaundice at diagnosis

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ABSTRACT

Purpose: The aim of this study was to elicit possible differences in prognoses and clinicopathological factors in pancreatic head cancer with and without obstructive jaundice at diagnosis.
Methods: The data from 169 patients with pancreatic head cancer were retrospectively analyzed.
Results: Patients were divided into two groups according to serum total bilirubin at diagnosis: ≥3 mg/dL for icteric group and <3 mg/dL for non-icteric group. In all cases, icteric group ($n = 104$) had a significantly worse prognosis than non-icteric group ($n = 65$) (median survival time (MST), 7.5 months (M) vs. 13.5 M, respectively; $P = 0.049$). In 84 resectable cases, icteric group had a significantly worse prognosis than non-icteric group (MST, 14.2 M vs. 20.9 M, respectively; $P = 0.049$) after almost equivalent treatment intensities. Icteric group had significantly larger T- and N-factors according to the UICC Classification compared to non-icteric group. The total number of lymph node metastases in icteric group was significantly larger than in non-icteric group ($P = 0.008$). The intrapancreatic nerve invasion in icteric group was significantly stronger than in non-icteric group ($P = 0.016$). There were no significant differences in the mortality and morbidity between icteric and non-icteric groups. In 85 unresectable cases, there was no significant difference between the survival periods of icteric and non-icteric groups (MST, 5.2 M vs. 5.3 M, respectively).
Conclusions: The presence of obstructive jaundice at diagnosis in patients with pancreatic head cancer may predict an unfavorable survival compared to such patients without obstructive jaundice.

1. Introduction

Pancreatic head cancer present as two clinically different phenotypes at diagnosis: patients with and without obstructive jaundice. This difference may be partly caused by the location of the tumor in relation to the intrapancreatic common bile duct. Other assumable triggers of obstructive jaundice are large tumor size and a greater degree of invasion.

Recently, the impact of preoperative biliary drainage (PBD) for icteric periampullary tumor on mortality and morbidity after pancreaticoduodenectomy (PD) has been well investigated.[1–8] Some investigators prefer PBD prior to PD because of its effects on surgical outcome or survival.[2,3,5] However, some investigators have demonstrated that infectious complications, notably wound infections, increase with PBD. They have therefore concluded that immediate PD is preferable, and PBD before PD should be selectively applied to patients suffering from cholangitis, patients who will receive neoadjuvant treatments, patients requiring a substantial time of preoperative assessment and operation schedule, or patients who need additional time for referral to a high volume center for PD.[6–8]

Regarding the impact of PBD on survival in patients with pancreatic head cancer who underwent PD, a few investigations have been reported. Smith and co-workers were the first to investigate this subject, and concluded that there were no differences in overall survival between groups who did and did not receive PBD.[9] Eshuis and colleagues reported that a delay in surgery associated PBD for patients with pancreatic head cancer did not affect the survival rate.[5]

The aim of the present study was to compare survival time and clinicopathological characteristics of patients between icteric and non-icteric pancreatic head cancer at diagnosis, apart from the impact of PBD on survival. This study included the unresectable cases besides the resectable cases.

2. Patients and methods

2.1. Patients

One hundred sixty nine consecutive patients with pancreatic head cancer admitted in Osaka City University Hospital from January 1990 to December 2009. No

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patients with periampullary tumors except pancreatic head cancer were included in this study. The median follow up time for these patients were 8.8 months (0.3–122 months). The cases included 84 resectable and 85 unresectable tumors. All 84 patients with resectable pancreatic head cancer in the present study had no hematogenous metastasis or peritoneal disseminations, and underwent PD. PD included pylorus-preserving PD and subtotal stomach-preserving PD.[10] Other resectable criterion for pancreatic head cancer beside no distant metastasis is no invasion to celiac/superior mesenteric/common hepatic artery. Portal invasion is not an unresectable criterion in our institute as well as most Japanese Department of Pancreatic Surgery. In order to observe survival time, patients who were admitted after January 2010 were not included in the present study.

2.2. Classification

Jaundice was defined as a serum bilirubin level ≥3 mg/dL, because patients above this value usually exhibited clinically evident jaundice through findings of yellowish skin and/or conjunctival membranes over the sclerae due to hyperbilirubinemia. Patients in the present study were therefore divided into two groups: those with a serum total bilirubin ≥3 mg/dL at diagnosis (icteric group) and those with a serum total bilirubin <3 mg/dL at diagnosis (non-icteric group). Among 65 patients of non-icteric group, 15 patients complained abdominal pain, 10 did back pain, six did appetite loss, and six did weight loss. Among 28 patients with no complains in non-icteric group, one patient was diagnosed for pancreatic cancer by medical checkup, and others were done during following up for other diseases such as diabetes mellitus, chronic pancreatitis, and hepatic hemangioma. Patients in non-icteric group were diagnosed for pancreatic cancer firstly with abdominal ultrasonography or abdominal computed tomography.

T- and N-factors were decided according to the International Union Against Cancer (UICC) Classification.[11] The definition of residual tumor after PD was made through the Japanese Pancreas Society's Classification of Pancreatic Cancer[12]; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor. The definitions of lymphatic invasion (ly), venous invasion (v), and intrapancreatic nerve invasion (ne) were also made through the Japanese Pancreas Society's Classification of Pancreatic Cancer; ly0, v0 and ne0 mean no invasion; ly1, v1 and ne1 mean slight invasion; ly2, v2 and ne2 mean moderate invasion; ly3, v3 and ne3 mean marked invasion.

2.3. Biliary drainage

With serum total bilirubin ≥3 mg/dL due to a periampullary tumor, biliary drainage (BD) is principally indicated for obstructive jaundice in our institution. Therefore, all patients in icteric group underwent BD. In our hospital, BD had been performed through percutaneous transhepatic cholangio-drainage (PTCD). Since 2006, most patients in our hospital have undergone endoscopic retrograde biliary drainage (ERBD) for BD. Among 12 patients who underwent BD in our hospital from January 2006 to December 2009, ERBD were successfully performed for 10 patients and PTCD were done for two patients. In the most of other hospitals, PTCD has still been performed as first choice treatment for the patients with obstructive jaundice before referring them to our hospital, because these hospitals had no endoscopists who could perform ERBD.

2.4. Statistical analysis

The Student's *t*-test was employed to compare the mean values between icteric and non-icteric groups. The chi-square test (or Fisher exact test) was used to compare the prevalence or distribution of two variables. Correlation was evaluated by the Spearman's rank correlation test. Survival data were estimated by the Kaplan–Meier method and examined by the log-rank test as a univariate survival analysis. The Cox proportional hazard model was employed for the multivariate analysis of survival. A *P*-value <0.05 was considered to indicate statistical significance.

Table 1
Comparison of treatment for all patients with pancreatic head cancer between groups stratified by serum total bilirubin at diagnosis ($n = 169$).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P*-value
	≥3 (Icteric group)	<3 (Non-icteric group)	
Number of patients	104	65	
Age (years)	65.1 ± 10.4 (34–90)	66.2 ± 10.5 (40–84)	0.512*
Male:Female	63:41	39:26	0.941**
Resectability	47.1%	53.8%	0.395**
Biliary drainage			
No	0	65	<0.001**
PTCD	85	0	
ERBD	19	0	
Serum total bilirubin at diagnosis (mg/dL)	11.4 ± 7.1 (3.0–44.8)	0.8 ± 0.5 (0.3–2.2)	<0.001*
Gemcitabine No:Yes	67:37	49:16	0.135**
5-Fluoropyrimidine No:Yes	71:33	36:29	0.090**
Radiation therapy No:Yes	76:28	40:25	0.116**

PTCD, percutaneous transhepatic cholangio-drainage; ERBD, endoscopic retrograde biliary drainage.
Numbers in parentheses are the ranges of values.
P-value was examined by the *Student's *t*-test or **chi-square test (Fisher's exact test).

3. Results

3.1. All case

The survival time of icteric group was significantly shorter than that of non-icteric group in 169 patients with pancreatic head cancer (Fig. 1). There were no significant differences in back ground characteristics (Table 1).

3.2. Resectable case

The survival time of icteric group was significantly shorter than that of non-icteric group in resectable pancreatic head cancer

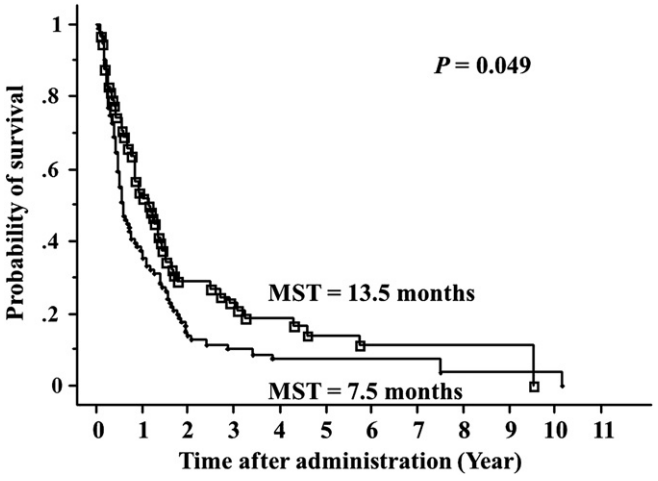

Fig. 1. Kaplan–Meier curve of patients with all patients with pancreatic head cancer stratified by serum total bilirubin at diagnosis (●, ≥3 mg/dL vs. □, <3 mg/dL). MST, median survival time.

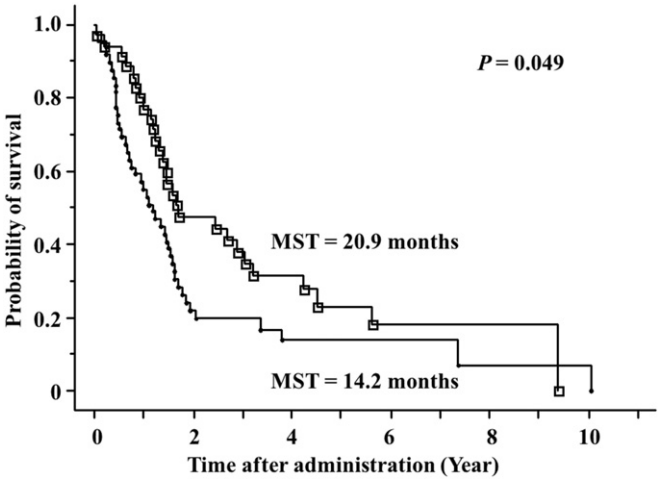

Fig. 2. Kaplan–Meier curve of patients with resectable pancreatic head cancer who underwent pancreaticoduodenectomy stratified by serum total bilirubin at diagnosis (●, ≥3 mg/dL vs. □, <3 mg/dL). MST, median survival time.

Table 2
Comparison of treatment for patients with resectable pancreatic head cancer between groups stratified by serum total bilirubin at diagnosis ($n = 84$).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P*-value
	≥3 (Icteric group)	<3 (Non-icteric group)	
Number of patients	49	35	
Age (years)	65.2 ± 11.0 (34–82)	66.4 ± 10.0 (40–84)	0.626*
Male:Female	26:23	20:15	0.711**
Preoperative biliary drainage			
No	0	35	<0.001**
PTCD	39	0	
ERBD	10	0	
Serum total bilirubin at diagnosis (mg/dL)	11.6 ± 6.8 (3.0–30.5)	0.8 ± 0.5 (0.3–2.2)	<0.001*
Total bilirubin at 1 day before operation (mg/dL)	1.5 ± 1.0 (0.3–4.9)	0.7 ± 0.4 (0.2–1.9)	<0.001*
Operation PD:PpPD:SSPPD	45:2:2	30:2:3	0.640**
Portal vein resection No:Yes	33:16	24:11	0.906**
Operation time (min)	493 ± 118 (285–925)	525 ± 174 (345–1350)	0.316*
Intraoperative blood loss volume (mL)	1628 ± 1094 (430–5710)	1838 ± 3473 (300–21,300)	0.693*
Intraoperative blood transfusion No:Yes	16:33	12:23	>0.999**
Intraoperative blood transfusion volume (mL)	1697 ± 1359 (0–7080)	1816 ± 4312 (0–21,560)	0.878*
Adjuvant gemcitabine No:Yes	44:5	32:3	>0.999**
Adjuvant 5-fluoropyrimidine No:Yes	31:18	18:17	0.278**
Intraoperative irradiation No:Yes	40:9	33:2	0.111**
Extracorporal irradiation No:Yes	45:4	33:2	>0.999**

PTCD, percutaneous transhepatic cholangio-drainage; ERBD, endoscopic retrograde biliary drainage; PD, pancreaticoduodenectomy; PpPD, pylorus-preserving PD; and SSPPD, subtotal stomach-preserving PD.
Numbers in parentheses are the ranges of values.
P-value was examined by the *Student's *t*-test or **chi-square test (Fisher's exact test).

(Fig. 2). There were no significant differences in PD method, rate of portal vein resection, operation time, or intraoperative blood loss/transfusion volumes between icteric and non-icteric groups. Adjuvant chemotherapy and radiation therapy were not different between the two groups (Table 2). Possible reasons for the poorer prognosis in icteric group were sought through examination of the differences in clinicopathological factors between icteric and non-icteric groups (Table 3). The tumor size between the two groups was not different. The T- and N-factors of icteric group were significantly larger than those of non-icteric group. The degree of residual tumor after operation for icteric group tended to be higher than that for non-icteric group. There were no differences in histology between icteric and non-icteric groups. The total number of lymph node metastases in icteric group was significantly higher

Table 3
Comparison of tumor progression at operation and recurrence site after operation in patients with resectable pancreatic head cancer between groups stratified by serum total bilirubin at diagnosis ($n = 84$).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P*-value	*ρ*-value
	≥3 (Icteric group)	<3 (Non-icteric group)		
Tumor size (cm)	3.2 ± 1.0 (1.2–5.0)	2.9 ± 1.1 (1.0–5.5)	0.181*	–
T-factor T1:T2:T3:T4	1:0:46:2	1:8:24:2	0.013#	0.272#
N-factor N0:N1	14:35	20:15	<0.009**	–
Residual tumor after operation R0:R1:R2	30:5:14	28:3:4	<0.055#	0.211#
Histology				
Well differentiated tubular adenocarcinoma	17	11	0.639**	–
Moderately differentiated tubular adenocarcinoma	23	20		
Poorly differentiated tubular adenocarcinoma	6	2		
Papillary adenocarcinoma	1	0		
Moderately differentiated adenosquamous carcinoma	0	1		
Mucinous carcinoma	1	1		
Undifferentiated carcinoma	1	0		
Total number of lymph node metastases	3.0 ± 3.8 (0–19)	1.1 ± 2.2 (0–9)	0.008*	–
Venous invasion v0:v1:v2:v3	29:12:6:2	27:7:1:0	0.054#	0.212#
Lymphatic invasion ly0:ly1:ly2:ly3	7:12:28:2	11:8:13:3	0.165#	0.152#
Intrapancreatic nerve invasion ne0:ne1:ne2:ne3	6:10:22:11	11:10:9:5	0.016#	0.264#
Recurrence site				
Peritoneum No:Yes	31:18	26:9	0.286**	–
Liver No:Yes	34:15	30:5	0.083**	–
Local No:Yes	37:12	27:8	0.863**	–
Lymph node No:Yes	41:8	27:8	0.452**	–
Lung No:Yes	46:3	33:2	>0.999**	–
Bone No:Yes	47:2	34:1	>0.999**	–

TNM classification is according to the International Union Against Cancer (UICC, 2009).
R-, v-, ly-, and ne-factors are expressed according to the Classification of Pancreatic Carcinoma by the Japanese Pancreas Society (2003).
Patients who had multiple recurrence sites were included in each recurrence site.
P-value wad examined by the *Student's *t*-test, the **chi-square test (Fisher's exact test) or the #Spearman's rank test.
ρ-value was calculated by the #Spearman's rank correlation test.

than that of non-icteric group. The degree of intrapancreatic nerve invasion of icteric group was significantly larger than those of non-icteric group. There were no specific recurrence sites for icteric or non-icteric groups except for inclination toward a higher rate of liver metastatic recurrence in icteric group compared to non-icteric group.

Univariate survival analysis indicated that icteric group, T4, N1, R1/2, and ne2/3 were significant predictors of a worse prognosis for patients with pancreatic head cancer who underwent PD (Table 4). By multivariate survival analysis, the factors of R1/2 alone were shown to have an independent prognostic impact on survival (Table 4).

Postoperative mortality and morbidity after PD between icteric and non-icteric groups were compared (Table 5). Two patients in both icteric and non-icteric groups died during their hospitalization after PD. There was no statistical difference in the rate of in-hospital mortality or reoperation between icteric and non-icteric groups. Regarding postoperative complications such as pancreaticojejunostomy leakage, choledochojejunostomy leakage, gastrojejunal bleeding, intraabdominal bleeding, cholangitis, ileus, and pneumonia, there were no statistical differences in incident rates between icteric and non-icteric groups.

Table 5
Comparison of in-hospital postoperative mortality and morbidity in patients with pancreatic head cancer between groups stratified by serum total bilirubin at diagnosis ($n = 84$).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P*-value
	≥3 (Icteric group)	<3 (Non-icteric group)	
Number of patients	49	35	–
In-hospital postoperative mortality No:Yes	47:2	33:2	>0.999
Reoperation No:Yes	46:3	34:1	0.637
Postoperative complication			
Pacreaticojejunostomy leakage No:Yes	48:1	33:2	0.568
Choledochojejunostomy leakage No:Yes	46:3	35:0	0.262
Gastrojejunal bleeding No:Yes	47:2	33:2	>0.999
Intraabdominal bleeding No:Yes	48:1	35:0	>0.999
Cholangitis No:Yes	45:4	33:2	>0.999
Ileus No:Yes	47:2	35:0	0.508
Pneumonia No:Yes	45:4	33:2	>0.999

P-value was examined by the chi-square test (Fisher's exact test).

3.3. Unresectable case

There was no difference of survival time between icteric and non-icteric groups in unresectable pancreatic head cancer (Fig. 3). There were no significant differences in inoperable factors such as involvement of superior mesenteric/celiac artery and distant metastasis. Regarding palliative operation, chemotherapy and radiation therapy, there were no differences between the two groups (Table 6).

4. Discussion

The primary purpose of this study was to examine the capability to predict survival time through the presence of obstructive jaundice at diagnosis in patients with pancreatic head cancer. Median survival time of 104 patients belonged to icteric group was significantly shorter than that of 65 patients belonged to non-icteric group under similar resectability and treatment backgrounds (Fig. 1, Table 1). These results suggest the icteric patients with pancreatic head cancer may have worse prognosis compared to those with non-icteric patients. It is notable that the resectability was not different between icteric and non-icteric groups.

It is well known that there is a large difference between the survival times of resectable and unresectable patients with pancreatic head cancer. Therefore, the survival data should be analyzed respectively in resectable and unresectable cases. Univariate analysis indicated a significantly poorer prognosis in icteric group compared to non-icteric group in resectable patients with the comparable treatment backgrounds (Fig. 2, Table 2). Contrary to our expectation, there was no significant difference in tumor size between the two groups (Table 3). The unfavorable prognosis of icteric group may be caused by the significantly larger T- and N-factors and the significantly stronger intrapancreatic nerve invasion compared to non-icteric group (Table 3). R-factor and venous invasion of icteric group tended to be higher than those of non-icteric group (Table 3). Actually, larger T-, N-, R-factors and stronger intrapancreatic nerve invasion were significant predictors of a worse prognosis by univariate survival analysis in the present study (Table 4). The previous investigations also have demonstrated that these factors were significant prognostic indicators.[13–15] However, by multivariate survival analysis, icteric group failed to be an independent predictor of worse survival in the present study (Table 4). The relatively higher rate of recurrence in the liver in icteric group compared to non-icteric group may also be attributed to the higher degrees of T- and N-factors and stronger intrapancreatic nerve invasion in icteric group (Table 3). These findings are summarized as that resectable pancreatic head cancer with obstructive jaundice preoperatively may have severer advanced tumor than non-icteric case. Consequently, the patient with

Table 4
Univariate and multivariate survival analysis of patients with resectable pancreatic head cancer who underwent pancreaticoduodenectomy ($n = 84$).

Variable	Comparison	Univariate			Multivariate		
		No. of patients	Median survival (months)	*P*-value*	Hazard ratio	95% confidence interval	*P*-value**
Serum total bilirubin at diagnosis	≥3 mg/dL vs. <3 mg/dL (Icteric group) vs. (Non-icteric group)	49:35	14.2:20.9	0.049	1.149	0.675–1.954	0.610
T-factor	T4 vs. T1, 2, 3	4:80	2.9:17.9	0.001	2.124	0.712–6.339	0.177
N-factor	N1 vs. N0	50:34	15.0:22.8	0.018	1.394	0.814–2.390	0.226
Residul tumor after operation	R1, 2 vs. R0	26:58	8.3:20.7	<0.001	2.594	1.496–4.499	<0.001
Intrapancreatic nerve invasion	ne2, 3 vs. ne0, 1	47:37	14.0:20.9	0.019	1.541	0.918–2.587	0.102

*P-values were examined by the log-rank test for univariate survival analysis.
**P-values were examined by the Cox proportional hazards model for multivariate survival analysis.
TNM classification is according to the International Union against Cancer (UICC, 2009).
R-and ne-factors are expressed according to the Classification of Pancreatic Carcinoma by the Japanese Pancreas Society (2003).

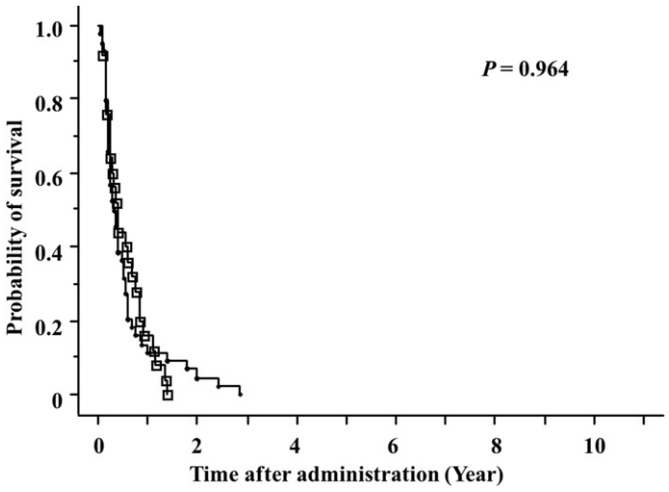

Fig. 3. Kaplan–Meier curve of patients with unresectable pancreatic head cancer stratified by serum total bilirubin at diagnosis (●, ≥3 mg/dL vs. □, <3 mg/dL). Median survival time: ●, 5.2 months; □, 5.3 months.

pancreatic head cancer and with preoperative obstructive jaundice may be a candidate for intensive treatment such as neoadjuvant treatment.

The rates of in-hospital mortality and reoperation in icteric group were not different from those of non-icteric group. Occurrence of life-threatening complications after PD was also not different between the two groups (Table 5). These results coincided with the previous findings that PBD was not associated with mortality and morbidity after PD,[1–4] because all patients of icteric group underwent PBD in the present study. A recent randomized trial comparing the clinical outcomes of PBD to those of early-surgery without PBD for patients with pancreatic head cancer who developed obstructive jaundice indicated no significant differences of surgery-related complications, mortality or the length of hospital stay between the two groups. However, the authors concluded that routine PBD for patients with pancreatic head cancer undergoing PD should be avoided because of the high rate of PBD-related complications (such as cholangitis, pancreatitis, duodenal perforation and hemorrhage after ERCP).[1] A majority of the most recent retrospective studies of patients with periampullary tumors and jaundice have demonstrated that there are no significant differences in mortality or morbidity after PD between patients with PBD and without PBD.[2–4] In those previous studies, all or the majority of the non-PBD patients exhibited high serum total bilirubin levels. This could be because the aim of those investigations was to examine the necessity of PBD for preoperative jaundice.[1–9] It is notable and distinguishable from the previous studies that all of the non-PBD patients in the present study had low serum total bilirubin levels less than 3 mg/dL.

Contrary to resectable cases, there was no survival difference between icteric and non-icteric groups in unresectable pancreatic head cancer (Fig. 3, Table 6). Unresectable patients have intensive locally advanced tumors and/or distant metastases at diagnosis and extremely short survival times both in icteric and non-icteric groups. Although the degrees of T-factor, N-factor, and intrapancreatic nerve invasion can not be assessed accurately in unresectable cases, these factors might be not different between icteric and non-icteric groups, resulting no survival difference.

In conclusion, the patients with pancreatic head cancer and with obstructive jaundice at diagnosis may have a worse prognosis compared to those patients without obstructive jaundice. In the subgroup analyses, a significant survival difference between icteric and non-icteric patients was seen in resectable cases, but not in unresectable cases. The worse prognosis of icteric patient after PD may be due to stronger tumor aggressiveness compared to non-icteric patient. Because PBD may not increase in-hospital death or the number of severe surgical complications after PD, patients with obstructive jaundice may benefit from intensive treatment including a neoadjuvant chemoradiotherapy after PBD.

Ethical approval

Written consents were obtained from the patients.

Funding

None.

Table 6
Comparison of inoperable factor and treatment for patients with unresectable pancreatic head cancer between groups stratified by serum total bilirubin at diagnosis ($n = 85$).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P*-value
	≥3 (Icteric group)	<3 (Non-icteric group)	
Number of patients	55	30	
Age (years)	65.0 ± 9.9 (54–90)	65.9 ± 11.3 (40–79)	0.682*
Male:Female	37:18	19:11	0.714**
Biliary drainage			
No	0	30	<0.001**
PTCD	46	0	
ERBD	9	0	
Serum total bilirubin at diagnosis (mg/dL)	11.2 ± 7.5 (3.0–44.8)	0.8 ± 0.6 (0.4–1.6)	<0.001*
Peritoneal dissemination No:Yes	45:10	22:8	0.360**
Hepatic metastasis No:Yes	26:29	15:15	0.810**
Invasion to superior mesenteric/celiac artery No:Yes	27:28	11:19	0.271**
Para-aorta/Virchow lymph node metastasis No:Yes	48:7	28:2	0.483**
Pulmonary metastasis No:Yes	52:3	28:2	>0.999**
Bone metastasis No:Yes	54:1	30:0	>0.999**
Choledocho-duodenal/jejunal anastomosis No:Yes	47:8	29:1	0.150**
Gastrojejunal anastomosis No:Yes	45:10	21:9	0.211**
Gemcitabine No:Yes	30:25	19:11	0.433**
5-Fluoropyrimidine No:Yes	41:14	18:12	0.164**
Radiation therapy No:Yes	40:15	19:11	0.369**

PTCD, percutaneous transhepatic cholangio-drainage; ERBD, endoscopic retrograde biliary drainage.
Numbers in parentheses are the ranges of values.
P-value was examined by the *Student's *t*-test or **chi-square test (Fisher's exact test).

Authors contributions

Study conception and design: Bunzo Nakata.

Acquisition of data: Bunzo Nakata, Ryosuke Amano, Kenjiro Kimura.

Analysis and interpretation of data: Bunzo Nakata.

Drafting of manuscript: Bunzo Nakata.

Critical revision of manuscript: Kosei Hirakawa.

Conflict of interest

All authors have no conflict of interest.

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