The impact of margin status determined by the one-millimeter rule on tumor recurrence and survival following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

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Abstract

Purpose: The tumor-node-metastasis (TNM) classification defines R1 as the presence of tumor cells at the resection margin, while the current Royal College of Pathologists (RCPath) guidelines for pancreaticoduodenectomy specimens regard the presence of tumor cells within 1 mm from the resection margin as R1 (the “1-mm rule”). The aims of this study were to investigate the resection margin status of pancreatic head cancer retrospectively according to both the TNM and 1-mm rule classifications, and to evaluate the postoperative survival and tumor recurrence patterns.

Methods: A total of 117 patients with pancreatic head cancer were the subjects of this study.

Results: $R1^{\text{1-mm rule}}$ resection was associated with a significantly worse disease-free survival (DFS) than $R0^{\text{1-mm rule}}$ resection (p=0.0259), while $R1^{\text{TNM}}$ had no impact on DFS. $R1^{\text{1-mm rule}}$ resection margin status correlated with the incidence of tumor recurrence in the liver (p=0.0483). In a multivariate analysis, $R1^{\text{1-mm rule}}$ resection was the independent variable for predicting poor DFS (hazard ratio, 1.71; p=0.0289). **Conclusions**: R1 resection margin status determined by the 1-mm rule may be an independent indicator for predicting disease recurrence, especially liver metastasis. These results may be useful for selecting the appropriate adjuvant therapy protocol and conducting strict surveillance in PDAC patients.

Keywords: Pancreatic ductal adenocarcinoma, margin, 1-mm rule, TNM, disease-free survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal and aggressive disease for which surgical resection remains the only potentially curative therapy. Many studies have investigated the postoperative predictors of survival, and some factors, such as the presence of lymph node metastases, have been found to be important postoperative prognostic factors for PDAC [1-12]. Microscopic tumor involvement of the surgical resection margin (R1) is one histopathological feature of the resected pancreatic specimen to have been reported to affect the PDAC patients' prognosis [1,2,4-16]. However, even with R0 resection (curative intent surgical resection), tumor recurrence has been reported to develop after surgery in over 60% of patients [11,14,15]. Therefore, true R1 status may be underestimated in pancreatic cancer.

Although accurate assessment of R1 resection status may provide useful information for selecting the appropriate adjuvant therapy protocol and strict surveillance for PDAC patients, international disagreement persists regarding the definition of R1 status. According to the 7th Tumor-Node-Metastasis (TMN) classification of the Union for International Cancer Control (UICC) [17] and the Japan Pancreas Society (JPS) reporting guidelines [18], R1 status is defined based on microscopic tumor exposure at any resection edge of the surgical specimen (TNM classification). In contrast, the British Royal College of Pathologists (RCPath) [19] recommends that cases with microscopic evidence of tumor extension to

within 1 mm of one or more resection margins be classified as R1 (“1-mm rule” classification).

Some studies have reported that the resection margin status of PDAC specimens according to the TNM classification had powerful prognostic significance for survival and recurrence [1,2,5,15]. However, the literature concerning the impact of resection margin status according to the 1-mm rule on the overall survival (OS) is gradually increasing in recent years [6-8,10-14,16]. Furthermore, the effect of 1-mm rule resection margin status on the disease-free survival (DFS) is still unclear [11].

The purpose of this study was, from the perspective of both the TNM classification and the 1-mm rule classification, to evaluate the impact of R1 resection margin status not only on the patient survival but also on disease recurrence.

Methods

Patients

All patients underwent surgery in the Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, during a 12-year period (between January 1, 1999, and December 31, 2010). None of the patients investigated in this study received chemotherapy or radiotherapy preoperatively. This study was limited to patients undergoing pancreaticoduodenectomy for resection of PDAC with no distant metastasis, and other lesions such as ampullary, duodenal, or distal bile duct adenocarcinomas and pancreatic adenocarcinomas arising within an intraductal papillary mucinous neoplasm were excluded. All patients underwent either subtotal stomach-preserving pancreaticoduodenectomy (91%) or pylorus-preserving pancreaticoduodenectomy (9%). The postoperative chemotherapy regimen included either tegafur-uracil (UFT), S-1 (oral fluoropyrimidine agent containing tegafur, gimeracil, and oteracil potassium), gemcitabine (GEM), or a combination of S-1 and GEM. Some patients did not receive the adjuvant chemotherapy in spite of R1 in postoperative pathological assessment. Postoperative radiotherapy for pancreatic cancer was generally not performed in our hospital. Follow-up information was obtained through a review of the patients' hospital medical records or from their primary physicians. Postoperative follow-up investigations consisted of a physical examination, laboratory studies, and computed tomography (CT)

imaging at 3- to 4-month intervals for the first 2 years, at 6-month intervals for years 3 through 5, and then at yearly intervals thereafter. This follow-up protocol was also applied as much as possible to most patients who received surgery at our hospital but were followed up at other centers. The median follow-up period for the censored patients was 46.5 months. Cancer recurrence was classified into three groups based on previous reports [4,15] as follows: local recurrence, which was defined as recurrence at the pancreatic resection site and root of the mesentery; regional recurrence, which was defined as recurrence in the soft tissues within the peritoneal cavity; and distant recurrence, which included liver metastases and other sites such as pulmonary, bone, and lymph node metastases or tumor marker elevation with no apparent recurrent findings on radiographic images. Informed consent was obtained from all patients preoperatively; this study was conducted in accordance with the ethical standards of the Committee on Human Experimentation of our institution.

Pathology Assessment

All resected specimens were dissected according to the General Rules for the Study of Pancreatic Cancer by the JPS [18], as follows: On receipt of the specimen fresh from the operating room, the duodenum was opened along the retroperitoneal side, and the bile duct was opened through the papilla of Vater. After orientation of the specimen, the key anatomical structures (e.g. ampulla, common bile duct, main pancreatic duct, and resection

margin) were identified in the presence of the operating surgeon. In this study, the resection margins, as previously reported [14], included the posterior and anterior surfaces, duodenal serosa, medial margin, and pancreatic, bile duct, and gastric/jejunal transection margins. After formalin fixation for 24-48 h, the specimen was sliced serially with about 5-mm-thick slices in a plane perpendicular to the duodenal axis. In our hospital, all of these dissected sections were assessed by senior pathologists according to the TNM staging system [17] and the General Rules for the Study of Pancreatic Cancer by the JPS [18].

The TNM classification described microscopically direct tumor exposure of the margin itself as R1 resection ($R1^{TNM}$ resection), with R0 resection ($R0^{TNM}$ resection) being anything else, with no evidence of tumor cells identified at any of the resection margins [17] (Fig. 1a). In contrast, the RCPath guidelines regard the presence of tumor cells ≤ 1 mm from the circumferential margin or surface of the pancreatic resection as R1 resection ($R1^{1\text{-mm rule}}$ resection); a resection margin status where tumor cells are more than 1 mm away from the resection margin is regarded as R0 resection ($R0^{1\text{-mm rule}}$ resection) [19] (Fig. 1b). In this study, loco-regional extension (i.e. lymph node metastases or perineural/lymphatic/vascular tumor propagation) ≤ 1 mm from a resection margin also constituted an R1 classification [9,13,14].

With careful patient selection and proper surgical technique, there were no R2 resections in pancreatic cancer, which is defined as a grossly incomplete resection [17,18], as recorded in the pathology reports, medical records, or operative dictations at our institution.

Based on the above, all of the histopathology slides were retrieved to classify resection margin status under the supervision of a single senior pathologist (T.M.). The resection margin was microscopically examined and measured from the nearest surgical resection margin to the tumor cells up to the submillimeter level.

Statistical Analysis

Categorical variables were compared using the chi-square test or Fisher's exact test depending on the sample size. The cumulative probability of overall survival (OS) and disease-free survival (DFS) was estimated by Kaplan-Meier survival methods, and differences between subgroups were assessed by the log-rank test. Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model. The level of significance was set at $P < 0.05$, and the confidence interval (CI) was determined at the 95% level. The statistical analysis was performed using the JMP 10.0 software program (SAS Institute, Inc., Cary, NC, USA) for Windows.

Results

Clinicopathological Characteristics and Resection Margin Status

A total of 117 patients were included in the study. The clinicopathological and resection margin status data for the study group are presented in Table 1.

When the TNM criteria (tumor exposure at resection margin) were applied, 22 (19%) of the 117 patients were histopathologically positive and thus were R1 resections ($R1^{TNM}$ resection). In $R1^{TNM}$ resection, 1 case (1/22; 5%) had multiple margin involvement. When the "1-mm rule" criteria were applied, 87 (74%) cases had histopathologically positive margins and were thus R1 resections ($R1^{1\text{-mm rule}}$ resection). In $R1^{1\text{-mm rule}}$ resection, 26 cases (26/87; 30%) had multiple margin involvement. In $R1^{TNM}$ resection, the pancreatic transection margin (41%) was the most commonly affected area of resection margin involvement, while in $R1^{1\text{-mm rule}}$ resection, the anterior surface (49%) was the most commonly affected area of resection margin involvement.

Relationship Between Survival and Resection Margin Status

Fig. 2 shows the Kaplan-Meier survival analysis according to the various margin classifications (OS: Fig. 2a, 2b, DFS: Fig. 2c, 2d). The median OS in patients with $R1^{TNM}$ resection was 12 months (95% confidence interval [CI], 8-16) vs. 17 months (95% CI, 13-22) in patients with $R0^{TNM}$ resection (p=0.0372). There was no significant difference in the OS

between $R1^{1\text{-mm rule}}$ and $R0^{1\text{-mm rule}}$ resections, at 14 months (95% CI, 11-17) vs. 20 months (95% CI, 11-40) (p=0.1329).

Similarly, there was no significant difference in the DFS between $R1^{TNM}$ and $R0^{TNM}$ resections, with the median survival being 7 months (95% CI, 3-10) and 8 months (95% CI, 7-11), respectively (p=0.0760). The median DFS in patients with $R1^{1\text{-mm rule}}$ resections was 7 months (95% CI, 6-10), vs. 10 months (95% CI, 6-40) in $R0^{1\text{-mm rule}}$ resection (p=0.0259).

Associations of Resection Margin Status with Tumor Recurrence

Associations of resection margin status with the incidence and location of tumor recurrence are summarized in Table 2. Cancer recurrence was significantly associated with $R1^{1\text{-mm rule}}$ resection status (p=0.0252), and a higher incidence of liver metastasis was observed in the $R1^{1\text{-mm rule}}$ resection group than in the $R0^{1\text{mm rule}}$ group (p=0.0483). Conversely, the proportion of patients with tumor recurrence was similar between the $R0^{TNM}$ and $R1^{TNM}$ resection groups (P=0.273).

Univariate and multivariate analyses for DFS of Resection Margin Status with the "1-mm rule" and clinicopathological factors

A univariate analysis for DFS using a Cox regression model identified vascular resection (p=0.0022), adjuvant therapy (p=0.0117), venous invasion (p=0.0119), tumor size (p=0.0141),

N stage (p=0.0249), R1[1-mm rule] resection margin status (p=0.0266), and lymphatic invasion (p=0.0342) as significant prognostic predictors. A multivariate analysis identified N stage (HR, 1.72; p = 0.0212), R1[1-mm rule] resection margin status (HR, 1.71; p=0.0289), adjuvant therapy (HR, 1.68; p = 0.0200), and vascular resection (HR, 1.58; p=0.0494) as the independent variables for predicting a poor DFS (Table 3).

Discussion

PDAC has a poor prognosis, and surgical resection remains the only effective therapy; however, resection for PDAC is often associated with the development of life-threatening intra-abdominal complications such as sepsis, abscesses, and early or delayed haemorrhaging [1-12,20-22]. While TNM classification and JPS reporting guidelines define margin involvement as tumor cell exposure at the surgical margin [17,18], the RCPath [19] has proposed the “1-mm rule”, which was at first advocated in rectal cancer [19,23,24], in the assessment of resection margin status of pancreatic cancer. However, unlike the data supporting the importance of a 1-mm circumferential resection margin in rectal cancers [23,24], the significance of resection margin status based on the 1-mm rule ($R^{1\text{-mm rule}}$) in predicting patient outcome and tumor recurrence in pancreatic cancer has been controversial [6-8,10-14,16].

There have been a few reports about the effect of margin status of pancreatic cancer, especially according to the 1-mm rule, on the mode of disease recurrence [11]. Jamieson et al. [9] noted no association between any stratification of resection margin clearance (from 0 to 2 mm, with 0.5-mm intervals) in 217 pancreaticoduodenectomy specimens and the site of recurrence. In contrast, in the present study, the incidence of tumor recurrence was clearly higher for liver metastases with the $R1^{1\text{-mm rule}}$ than with $R0^{1\text{-mm rule}}$. Differences may exist in the postoperative follow-up protocol between that study and the present study, particularly

with respect to the frequencies of CT or other imaging modalities. For example, Jamieson et al. [9] did not routinely perform postoperative imaging while the patient remained asymptomatic; however, we routinely performed postoperative CT, combined with other appropriate imaging modalities such as ultrasonography (US) or magnetic resonance imaging (MRI) if necessary, to detect tumor recurrence every 6 months, so the present recurrence data might be more sensitive than that obtained in earlier studies.

The results of the present study revealed a local recurrence rate of 21.7%, which is considerably lower than those of other reports (local recurrence rate: 60%–80% [11]) and leads us to believe that surgery achieves good local control. We believe that this is the reason R1 surgery did not show a significant correlation with the local recurrence rate and peritoneal dissemination. However, in cases of R1 surgery, the tumor is considered to have a high probability of invading adjacent tissues, with greater incidence of tumor cell invasion from the vessels to systemic circulation. This may have resulted in the significant increase in liver metastases noted in the present study. Our findings suggest that future adjuvant treatment regimens should be tailored depending on the resection margin status with a possibly different pattern of tumor recurrence.

Little has been reported about the effect of margin status determined by the 1-mm rule classification on DFS. To our knowledge, only John et al. [10] have described the relationship between resection margin status and DFS for resected pancreatic head cancer, and they found

that the $R1^{1\text{-mm rule}}$ had no impact on patient outcomes [10]; however, their report lacked postoperative chemotherapy data, which has been suggested to be strongly correlated with the patient outcome. In our opinion, the prognostic relevance of the R status remains controversial. The current study, to our knowledge, is the first to demonstrate in a multivariate analysis that $R1^{1\text{-mm rule}}$ resection was an independent variable for predicting a poor DFS.

In the present study, $R1^{TNM}$ status had a significantly worse prognosis for OS than did $R0^{TNM}$ status. In contrast, the DFS was not significantly different between $R1^{TNM}$ and $R0^{TNM}$. The reason for the poor OS prognosis despite there being no significant difference in recurrence timing may be that the $R1^{TNM}$ status included cases that rapidly progressed after recurrence and/or cases for which post-recurrence treatment was ineffective. In contrast, when the 1-mm rule was applied in the R staging, significant differences were observed in the DFS but not in the OS outcomes. When applying the 1-mm rule, the $R1^{1\text{-mm rule}}$ status included cases in which microscopic tumor infiltration was seen within 1 mm of the resected margins despite there being no tumor exposure to the resection stump or cut surface. Therefore, $R0^{1\text{-mm rule}}$ may be limited to low-grade malignant cases, e.g. those with microscopic tumor clearance after resection. As a result, fewer cases may have been designated as $R0^{1\text{-mm rule}}$, thus explaining the significant difference between $R1^{1\text{-mm rule}}$ and $R0^{1\text{-mm rule}}$ status in DFS. However, when using the 1-mm rule, a larger proportion of cases

with favorable prognosis due to effective post-recurrence treatment was included in R1. This may have been why no significant difference between $R1^{1\text{-mm rule}}$ and $R0^{1\text{-mm rule}}$ status was seen in OS.

The most likely reason for the varying results among R status studies is the method used for the pathologic evaluation of the resected specimens, which was not standardized. As for the handling of the resected specimens, in order to identify the anatomical structures precisely, inking of the circumferential margins or surface of the resected specimens is generally performed in Western countries [4-7,9,10,12-15]. At our hospital, the handling of the resected specimens, such as anatomic identification, has consistently been conducted by cooperation between the pathologists and operating surgeons without inking the specimens. In this manner, the current study found R1 rates of 19% and 74% in patients according to the TNM and 1-mm rule classification, respectively, which were generally consistent with the previous reports using the inking protocol [1,2,4-16].

Despite our interesting results, we acknowledge the limitations of this study. In addition to the single-center analysis, the present series included a relatively small number of patients compared with previous reports [1-7,9,11,14-16], and the study was retrospective in nature. Multi-center prospective analyses with larger patient numbers are needed in the future. Furthermore, we did not investigate the effects of adjuvant therapy on the postoperative survival and tumor recurrence patterns, especially focusing on the chemotherapy protocol,

because in this study, the postoperative chemotherapy regimens were not standardized (UFT, S-1, GEM, or a combination of S-1 and GEM). Future studies will be needed to explore this matter further.

In conclusion, this is the first report to demonstrate that an R1 resection margin status according to the 1-mm rule classification is a significant predictor of disease recurrence, especially liver metastases. These results may be useful for selecting the appropriate adjuvant therapy protocol and conducting strict surveillance in PDAC patients.

Conflict of interest

The authors declare no conflicts of interest in association with this study.

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Figure captions

Figure 1. A photomicrograph showing (a) $R1^{TNM}$ resection, with microscopically direct tumor exposure of the margin itself, and (b) $R1^{1\text{-mm rule}}$ resection, with tumor cells ≤ 1 mm from the circumferential margin or surface of the pancreatic resection. Arrows, tumor cells; dotted line, resection margin line

Figure 2. Kaplan-Meier cumulative survival curves according to the resection margin status. (a) The OS curves of the $R0^{TNM}$ and $R1^{TNM}$ resection groups. (b) The OS curves of the $R0^{1\text{-mm rule}}$ and $R1^{1\text{-mm rule}}$ resection groups. (c) The DFS curves of the $R0^{TNM}$ and $R1^{TNM}$ resection groups. (d) The DFS curves of the $R0^{1\text{-mm rule}}$ and $R1^{1\text{-mm rule}}$ resection groups.

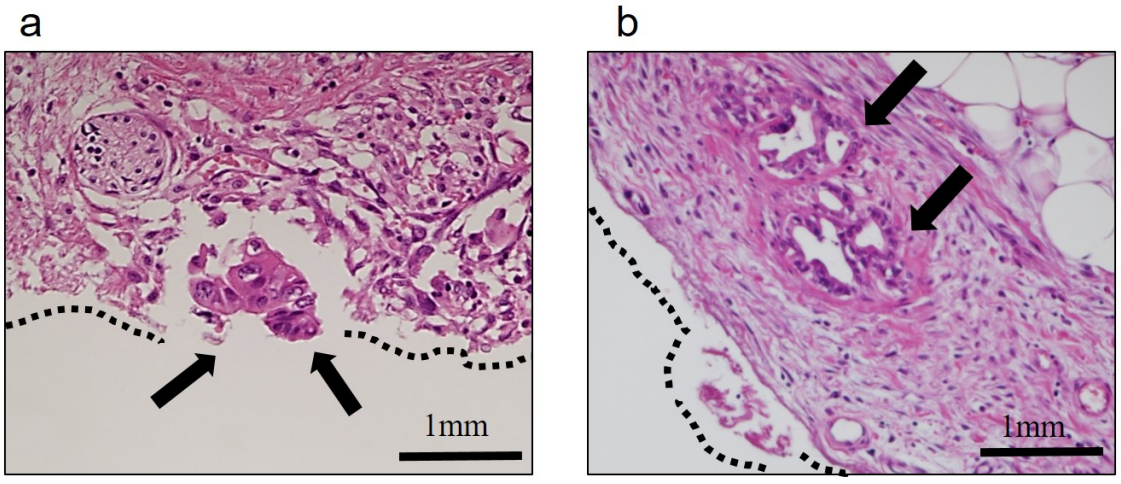

Figure 1.

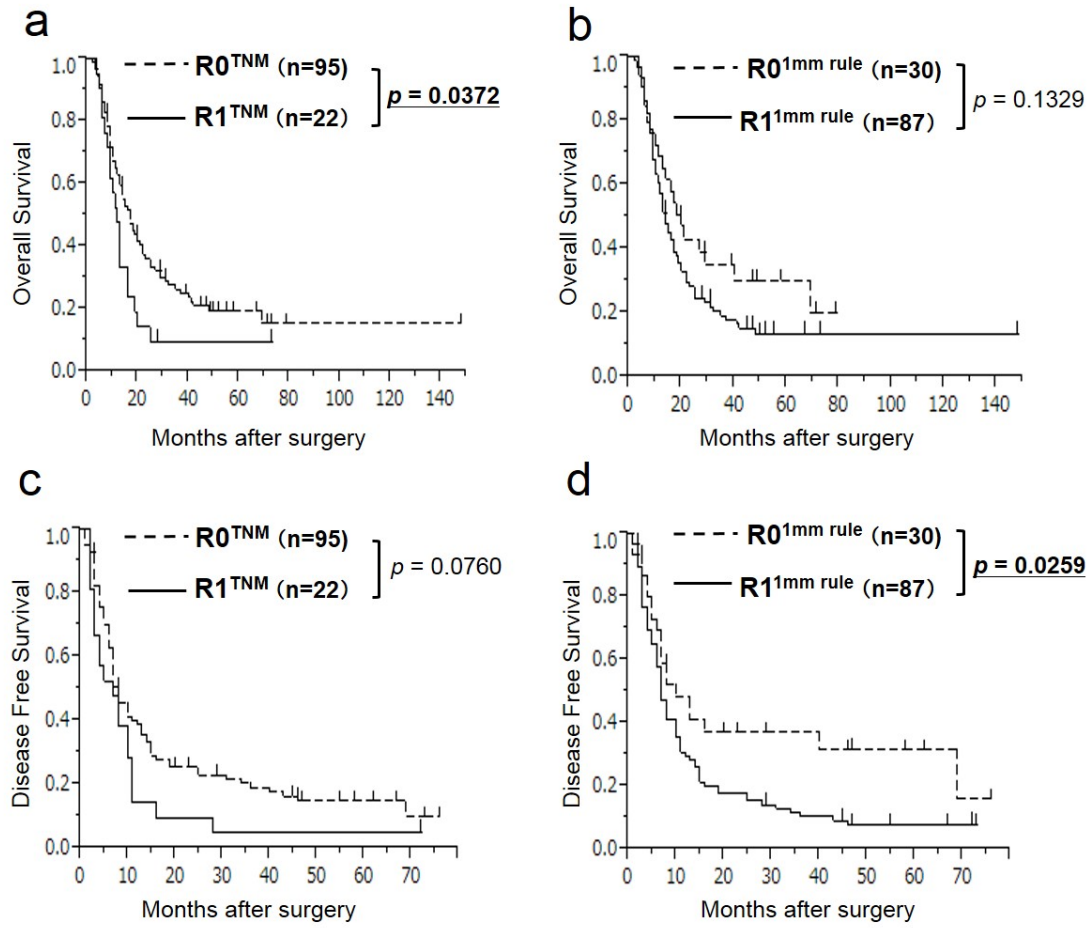
a
R0TNM (n=95)
R1TNM (n=22)
p = 0.0372
Overall Survival
Months after surgery
b
R01mm rule (n=30)
R11mm rule (n=87)
p = 0.1329
Overall Survival
Months after surgery
c
R0TNM (n=95)
R1TNM (n=22)
p = 0.0760
Disease Free Survival
Months after surgery
d
R01mm rule (n=30)
R11mm rule (n=87)
p = 0.0259
Disease Free Survival
Months after surgery

Figure 2.

TABLE 1. Clinicopathological characteristics and resection margin status of 117 patients undergoing resection for pancreatic head cancer

Clinicopathologic variables	**Number (%)**
Age, years (Median, Range)	66, 35-89
Sex (Male/Female)	72 (62)/45 (38)
T stage (T1, T2/T3, T4)	4 (3)/113 (97)
N stage (N0/N1)	33 (28)/84 (72)
Tumor size; cm (Mean ± SD)	3.3 ± 1.1
Tumor grade (Pap, Well, Mod/Poor+Others[*)]	94 (80)/23 (20)
Perineural invasion (No/Yes)	8 (7)/109 (93)
Venous invasion (No/Yes)	16 (14)/101 (86)
Lymphatic invasion (No/Yes)	41 (35)/76 (65)
Operation (SSPPD/PpPD)	107 (91)/10 (9)
Vascular resection (No/Yes)	43 (37)/74 (63)
Adjuvant therapy (No/Yes)	71 (61)/46 (39)
Cancer recurrence (No/Yes)	30 (26)/87 (74)
Resection margin status	**Number (%)[**]**
R0/R1 (TNM classification)	95 (81)/22 (19)
Number of involved resection margins	
1/2/3 or more	21 (95)/1 (5)/0 (0)
Distribution of resection margin involvement	
Posterior/Anterior/Duodenal surface	3 (14)/4 (18)/0 (0)
Medial/Pancreatic/Bile duct transection	6 (27)/9 (41)/1 (5)
Gastric/Jejunal transection	0 (0)/0 (0)
R0/R1 (1-mm rule)	30 (26)/87 (74)
Number of involved resection margins	
1/2/3 or more	61 (70)/19 (22)/7 (8)
Distribution of resection margin involvement	
Posterior/Anterior/Duodenal surface	34 (39)/43 (49)/0 (0)
Medial/Pancreatic/Bile duct transection	30 (34)/12 (14)/1 (1)
Gastric/Jejunal transection	0 (0)/0 (0)

Mod, moderately differentiated adenocarcinoma; Poor, poorly differentiated adenocarcinoma; PpPD, pylorus-preserving pancreaticoduodenectomy; Pap, papillary adenocarcinoma; SD, standard deviation; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; TNM, tumor-node-metastasis; Well, well-differentiated adenocarcinoma

[*]Others include adenosquamous carcinoma and undifferentiated carcinoma.

[**] The numbers include overlap in patients.

TABLE 2. Incidence and locations of recurrence by resection margin status in 117 patients undergoing resection for pancreatic head cancer

	Number (%)			Number (%)		
	$R0^{TNM}$	$R1^{TNM}$	*p*	$R0^{1mm\ rule}$	$R1^{1mm\ rule}$	*p*
Total number of patients	95 (81)	22 (19)		30 (26)	87 (74)	
Cancer recurrence			0.2731 [a]			**0.0252**
No	26 (27)	3 (14)		12 (40)	17 (20)	
Yes	69 (73)	19 (86)		18 (60)	70 (80)	
Site of recurrence						
Local recurrence			0.0569			0.6080[a]
No	78 (82)	14 (64)		25 (83)	67 (77)	
Yes	17 (18)	8 (36)		5 (17)	20 (23)	
Regional[b] recurrence			0.7330 [a]			0.5521[a]
No	81 (85)	20 (91)		25 (83)	76 (87)	
Yes	14 (15)	2 (9)		5 (17)	11 (13)	
Liver metastases			0.4772			**0.0483**
No	57 (60)	15 (68)		23 (77)	49 (56)	
Yes	38 (40)	7 (32)		7 (23)	38 (44)	
Others[c]			1.0000 [a]			0.2925
No	80 (84)	19 (86)		23 (77)	74 (85)	
Yes	15 (16)	3 (14)		7 (23)	13 (15)	

The numbers include overlap in patients.

[a]Fisher's exact test was used.

[b]Regional recurrence corresponds to recurrence in the soft tissues or lymph nodes within the peritoneal cavity.

[c]Others include pulmonary, bone, and distant lymph node metastases or tumor marker elevation with no apparent reccurent findings on radiographic images.

TABLE 3 Univariate and multivariate analyses of factors affecting the disease-free survival (DFS)

	Univariate			Multivariate		
Prognostic Variables	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)						
> 65	1.00	-	0.6455			
≤ 65	1.09	0.73 - 1.63				
Gender						
Female	1.00	-	0.5113			
Male	1.14	0.76 - 1.76				
T stage						
T1+T2	1.00	-	0.2999			
T3+T4	1.74	0.65 - 7.13				
N stage						
N0	1.00	-	**0.0249**	1.00	-	**0.0212**
N1	1.64	1.06 - 2.61		1.72	1.08 – 2.81	
Tumor size						
≤ 3.3 cm	1.00	-	**0.0141**	1.00	-	0.1531
> 3.3 cm	1.65	1.11 - 2.47		1.36	0.89 - 2.06	
Tumor grade						
Well+Pap+Mod	1.00	-	0.0740			
Poor+Others	1.60	0.95 - 2.57				
Perineural invasion						
No	1.00	-	0.0583			
Yes	2.17	0.97 - 6.18				
Venous invasion						
No	1.00	-	**0.0119**	1.00	-	0.1683
Yes	2.15	1.17 - 4.42		1.62	0.82 - 3.49	
Lymphatic invasion						
No	1.00	-	**0.0342**	1.00	-	0.7421
Yes	1.57	1.03 - 2.45		1.08	0.68 - 1.74	
Vascular resection						
No	1.00	-	**0.0022**	1.00	-	**0.0494**
Yes	1.92	1.25 - 3.00		1.58	1.00 - 2.56	
Adjuvant therapy						
Yes	1.00	-	**0.0117**	1.00	-	**0.0200**
No	1.69	1.12 - 2.61		1.68	1.08 - 2.64	
Resection margin status						
R0 (TNM)	1.00	-	0.1064			
R1 (TNM)	1.53	0.90 - 2.45				
R0 (1-mm rule)	1.00	-	**0.0266**	1.00	-	**0.0289**
R1 (1-mm rule)	1.70	1.06 - 2.86		1.71	1.05 - 2.90	

Mod, moderately differentiated adenocarcinoma; Poor, poorly differentiated adenocarcinoma; Pap, papillary adenocarcinoma; TNM, tumor-node-metastasis; Well, well-differentiated adenocarcinoma; HR, hazard ratio; 95% CI, 95%

confidence interval