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Evaluation of circumferential resection margins for pancreatic head cancer: A prospective study with a comparison between the 0 mm and 1 mm rules for R1 resection

췌장두부암의 주변 절제연에 대한 평가: 0 mm 대 1 mm R1 절제연 규칙을 비교한 전향적 연구

2022년 2월

서울대학교 대학원
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이 논문을 의학석사 학위논문으로 제출함

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김문환의 의학석사 학위논문을 인준함

2022년 1월

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Abstract

Evaluation of circumferential resection margins for pancreatic head cancer: A prospective study with a comparison between the 0 mm and 1 mm rules for R1 resection

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Background: Although microscopic residual disease (R1 resection) has been reported as an independent prognostic factor for pancreatic ductal adenocarcinoma (PDAC), the prognostic significance of R1 resection for PDAC has varied in the literature. The numerous variations may be due to the following reasons: 1) a lack of consensus on the definition of R1 resection (1 mm rule vs. 0 mm rule), 2) a lack of consensus on the definition of various resection margins and surfaces (e.g. anterior, posterior, superior mesenteric vein/portal vein [SMV/PV] and superior mesenteric

artery [SMA]), and 3) various grossing techniques in the pathology laboratory where pancreaticoduodenectomy (PD) specimens are being studied and analyzed.

Materials and Methods: We performed a prospective clinicopathological analysis of 111 cases of PDACs that were resected via PD. These specimens included those with venous resection (n = 36) and those without (n = 75). These patients underwent PD between March 2014 and December 2018 at the Seoul National University Bundang Hospital. All circumferential margin/surface of the pancreas (anterior, posterior, SMV/PV groove, and SMA), pancreatic neck margin, bile duct margin, and intestinal margins were painted using standardized ink color codes and were sectioned via the axial slicing method. The entire pancreatic head was submitted for histopathological mapping, and the safety margins for all margin/surface were recorded in millimeters. The patients were followed up for up to 69 months (median: 23 months), and the margin status was correlated with the patient outcome, including overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and post-operative complications. Moreover, surfaces were classified into either anterior or posterior, whereas resection margins were classified into pancreatic neck, SMV/PV groove, or SMA margins.

Results: Of the 111 specimens, 26 (23.4%) and 91 (82.0%) were regarded as R1 by the 0 mm rule and the 1 mm rule, respectively. Female sex (p = 0.035, hazard ratio [HR] = 1.853, 95% confidence interval [CI] = 1.043-3.291), histologic differentiation (moderate and poorly differentiated) (p = 0.004, HR 3.061, 95% CI = 1.427-6.570), and 0 mm R1 in resection margin (p = 0.001, HR = 3.178,

95% CI = 1.628−6.203) were identified as independent risk factors for OS. For DFS, only 0 mm R1 in resection margin [p = 0.013, HR = 3.595, 95% CI = 1.308−9.885) was an independent prognostic factor. When each circumferential margin/surface was analyzed using the recurrence rate by the 0 mm and 1 mm rules, the pancreas neck margin was involved in 5 (4.5%) and 12 (10.8%) cases; the anterior surface was involved in 3 (2.7%) and 35 (31.5%) cases; the posterior surface was involved in 8 (7.2%) and 43 (38.7%) cases; the SMV/PV groove was involved in 15 (13.5%) and 74 (66.7%) cases; and the SMA margin was positive in 8 (7.2%) and 38 (34.2%) cases; and any margin was positive in 26 (23.4) and 91 (82.0) cases, respectively. The presence of SMA margin involvement was significantly associated with local recurrence after surgery, if the 0 mm (p = 0.036) rule was applied.

Conclusion: A positive margin defined by the 0 mm rule was an independent risk factor for OS and DFS. An R1 SMA margin was associated with an increased risk of local recurrence rather than systemic recurrence. In comparison, a positive margin by the 1 mm rule was not associated with OS and DFS. These findings suggest that the 0 mm rule is more appropriate in predicting recurrence and survival than 1 mm rule. To confirm our findings, a well−designed large−scale study is needed.

Keywords: Pancreas head cancer, resection margin, margin status, pancreaticoduodenectomy, pancreas ductal adenocarcinoma
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Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

1.1. Study Background

Microscopic residual disease, or R1 resection, has been reported as an independent prognostic factor for pancreatic ductal adenocarcinoma (PDAC). However, the prognostic significance of R1 resection for PDAC varies in the literature. These variations may be due to the following reasons; 1) a lack of consensus on the definition of R1 resection (1 mm rule vs. 0 mm rule), 2) a lack of consensus on the definition of various resection margins and surfaces (e.g. anterior, posterior, superior mesenteric vein [SMV]/portal vein [PV] and superior mesenteric artery [SMA]), and 3) employment of various grossing techniques in the pathology laboratory for pancreaticoduodenectomy specimens.

The 1 mm R1 rule states that the presence of tumor cells at or within 1 mm from the inked margin is defined as a positive margin, which is also known as R1 resection (1). This was an extrapolation of the R1 definition for circumferential resection margins of rectal cancers. However, the pattern of tumor cell infiltration in rectal cancer is histologically different for pancreatic adenocarcinoma. In pancreatic adenocarcinoma, the tumor cells are more dispersed and discontinuous or scattered and separated by abundant connective tissue (2). Campbell et al. (3) demonstrated that the presence of tumor within 1 mm of the inked margin was associated with decreased overall survival. Moreover, they reported that there was no significant difference between the 0 mm and 1 mm margin status. It was concluded that microscopic tumor involvement within 1 mm should be considered synonymous with incomplete excision for resected pancreatic cancers. At that time, the SMA margin was not

specified and the anterior side of the pancreas was not included. The definition of R1 has varied according to the geographic region, for example, the 1 mm rule has been adopted in the UK and European countries earlier, while the 0 mm rule was the standard in other countries. However, there is an increasing consensus that the 1 mm rule is more important. In 2017, the CAP and the AJCC stated in their protocols that "the presence of tumor at or within 1 mm of a resection margin constitutes a positive margin."

The anterior surface of the pancreas in the pancreaticoduodenectomy (PD) specimen is smooth and bulging. This surface constitutes the posterior wall of the lesser sac. The SMV/PV or the vascular groove is the indentation caused by the SMV/PV. It is manually teased apart. In addition, it comes off readily during the operation. The SMA or uncinate margin, in contrast, is surgically dissected. The SMA margin is the plane of abutment of the uncinate process with the SMA. Only a scant buffer of connective tissue separates the uncinate process from the SMA, the neural plexus, and the lymphatic plexus around the celiac trunk. Therefore, this margin is at highest risk for residual disease (4). The posterior side is flat and is not surgically dissected. It overlies the retroperitoneal fat and the major blood vessels, such as the inferior vena cava (IVC).

Although there is universal agreement that the pancreatic neck margin, gastrointestinal margins, and bile duct margin of a PD specimen are true resection margins, there is still controversy as to what constitutes a margin or a surface for the various surfaces of the pancreas. The SMA margin, also called the retroperitoneal or uncinate margin, is acknowledged to be a resection margin. Reporting this margin is required in the recent revision of the CAP

protocol and the AJCC cancer staging manual. However, while the CAP, AJCC, and some other studies regard the anterior, posterior, and vascular grooves as “surfaces”, studies mainly based in Europe and the Royal College of Pathologists regard these structures as margins (5).

Meanwhile, Negel et al. (6) reported that R1 in the surface was not an independent risk factor for OS. According to Negel et al. (6), the anterior and posterior surfaces were not true margins because surfaces were not surgically dissected. In addition, they could be considered analogous to the serosal surface of the gastrointestinal tract. Therefore, the prognostic effect of the R1 surfaces in PDAC after PD was controversial.

Previous studies stated that resection margins/surfaces either be present individually or as a whole. Most studies did not analyze the R1 resection using both the 0 mm and 1 mm rules. The effect of these resection margins/surfaces and their involvement require meticulous analysis to arrive at more accurate results.

1.2. Purpose of the Research

In this prospective study, we sought to evaluate the clinicopathological and prognostic significances of the individual surfaces of the PD specimen and to evaluate the significance of the margin or surface involvement status according to the 0 mm and 1 mm rules.

Chapter 2. Body

2.1. Methods

Patients

A total of 140 patients with adenocarcinoma of the pancreatic head or uncinate process were enrolled in this prospective study, which was conducted between March 2014 and December 2018 at the Seoul National University Bundang Hospital. A total of 39 patients were excluded due to the following reasons: (1) they underwent palliative surgery (n = 1), (2) they underwent neoadjuvant chemotherapy (n = 15), (3) they had adenosquamous carcinoma (n = 7), or (4) they had mucinous carcinoma (n = 6). A total of 111 patients were finally included.

Pathological protocol

All pancreaticoduodenectomy specimens were examined according to the Leeds Pathology Protocol at the Department of Pathology. All circumferential margins and surfaces of the pancreas (pancreas neck, anterior, posterior, SMV/PV groove, SMA) were painted using standardized ink color codes, and the specimens were sectioned axially at 5 mm−intervals, perpendicular to the duodenal longitudinal axis (Figure 1). The entire pancreatic head was submitted for histopathological mapping, and the transected margins (pancreatic neck, bile duct, and gastrointestinal proximal and distal margins) were also inked and sampled (Figure 2). The same gross protocol was used for specimens with vein resection (VR), but the vascular transection margins were separately inked prior to axial sectioning. The safety margins for all margins and surfaces were defined as the closest distance between tumor cells and the inked

margin or surface and were recorded in millimeters. For specimens with VR, their margins and the SMV/PV groove above and below the attached vein were analyzed. At the time of diagnosis, the 0 mm rule was used for reporting purposes. However, the safety margin was stated for each margin/surface, and for patients where the safety margin was less than 1 mm, the margins were reported as "<1 mm" or in μm. For this study, "positive margin by the 0 mm rule" was defined as the presence of tumor cells at the inked margin/surface. The "positive margin by the 1 mm rule" was defined as the presence of tumor cells within 1 mm from the inked margin/surface. The "anterior and posterior surface" was defined as a surface. Finally, the "pancreas neck, SMV/PV groove and SMA margin" was defined as a resection margin.

Data collection

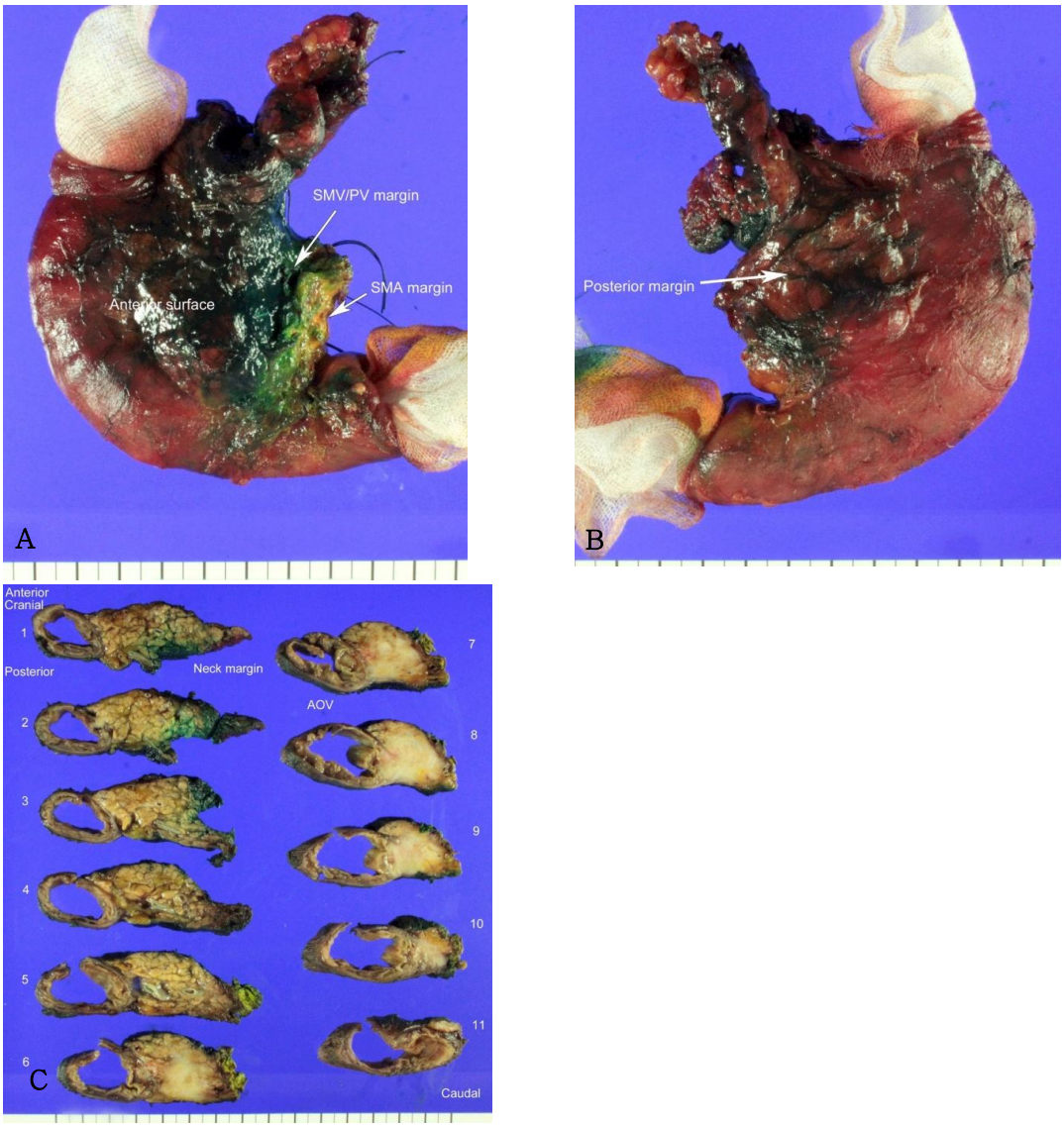
The following clinicopathological data were obtained for each case by reviewing the electronic medical records, pathology reports, and glass slides. The following data were obtained: age at operation, sex, type of operation, tumor size, resection margin status, site of local recurrence, site of distant metastasis, neoadjuvant treatment, postoperative treatment, preoperative serum CEA and CA19-9 levels, pathological diagnosis, histologic differentiation, gross type, pT and pN stages according to the AJCC TNM staging system, 8th edition, number of positive lymph nodes, total number of lymph nodes, lymphatic, venous or perineural invasion, presence of chronic pancreatitis, involvement of adjacent organs (bile duct, duodenum or other organs), post-operative complications (Clavien-Dindo classification) and performance status (ECOG, ASA). Follow-up data were obtained from the electronic medical

records. Overall survival (OS) was defined as the interval between surgery and death of any cause, while disease-free survival (DFS) was defined as the interval between surgery and local recurrence or distant metastasis. Local recurrence free survival (LRFS) was defined as the interval between surgery and local recurrence. Moreover, distant metastasis free survival (DMFS) was defined as the interval between surgery and distant metastasis. Local recurrence and distant metastasis were diagnosed on follow-up imaging.

Statistical analysis

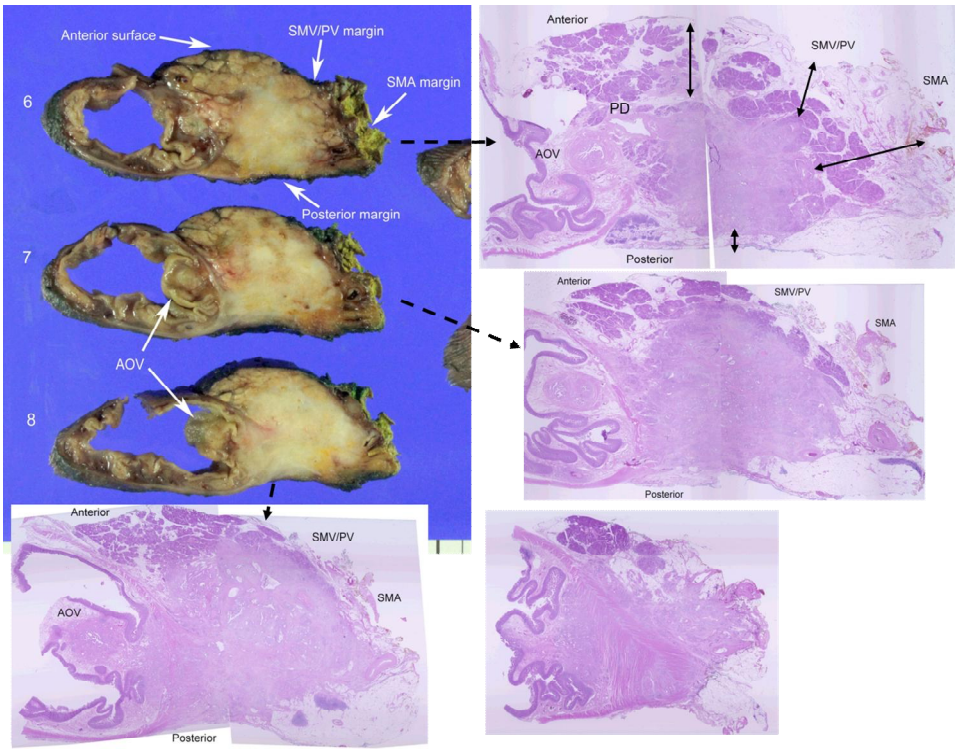
Statistical analyses were performed using the SPSS for Windows version 25.0K (SPSS Korea, Seoul, Republic of Korea). Categorical data were analyzed using the chi-squared and Fisher exact tests as deemed appropriate. Survival analyses for OS and DFS were performed via the Kaplan-Meier method and log-rank test. Variables found to be significant on univariate analysis were further analyzed for multivariate analysis using the Cox regression model. Statistical significance was defined as $p < 0.05$.

Figure 1. Pancreaticoduodenectomy specimen orienting and grossing protocol



A. The anterior surface is shown. The SMV/PV and SMA margins are visible. B. This is the posterior surface C. This is a gross axial review directed cranio-caudally.

Figure 2. Histological evaluation of the circumferential resection margins and surfaces



Histologic slides at each transection level. The white arrow indicates the gross margin, while the black arrow indicates the histologic margin.

2.2. Results

Baseline clinicopathological characteristics

The clinicopathological characteristics of 111 patients are described in Table 1. The patients comprised 60 men and 51 women with a mean age of 68.7±10.9 years. The preoperative CEA and CA19.9 were 3.9±9.9 ng/ml and 438.5±775.1 U/ml. The performance statuses were expressed using the Eastern Cooperative Oncology Group (ECOG) and American Society of Anesthesiologists (ASA) scores. A score of 1 was evident in 97 patients (87.4%), while ASA 2 was evident in 84 (75.7%). PPPD was a more common procedure, and combined VR was performed in 36 (32.4%) patients. The most common pathology was PDAC (91.9%), and intraductal papillary mucinous neoplasm was associated in 9 (8.1%) patients. The mean tumor size was 3.0±0.9 cm. The most common histologic grade was moderate differentiation (57.7%). Lymphatic, venous, and perineural invasion were present in 85 (76.6%), 50 (45.1%) and 104 (93.7%) patients, respectively. Most patients (80.1%) had a T2 stage. LN metastasis was found in 86 (77.4%) patients (N1, 42.3%; N2, 35.1%). The mean numbers of positive and harvest lymph nodes were 3.1±3.2 and 21.8±8.5, respectively. At least one positive resection margin/surface by the 0 mm and 1 mm rules was observed in 26 (23.4%) and 91 (82.0%) patients, respectively. Adjuvant treatment was performed in 90 (81.1%) patients.

Table 1. Clinicopathological data of the cohort

	All patients (n=111)
Age, years	68.7±10.9
Sex (male/female), n (%)	60 (54.0) / 51 (46.0)
Preoperative CEA, ng/ml,	3.9±9.9
Performance status, n (%)	
ECOG	
0	97 (87.4)
1	14 (12.6)
ASA	
1	12 (10.8)
2	84 (75.7)
3	15 (13.5)
4	0 (0)
Preoperative CA19-9, U/ml,	438.5±775.1
Type of operation, n (%)	
PPPD	86 (77.5)
Whipple	25 (22.5)
Combined VR	36 (32.4)
Pathological diagnosis, n (%)	
Ductal adenocarcinoma	102 (91.9)
IPMN with associated invasive carcinoma	9 (8.1)
Tumor size, cm	3.0±0.9
Differentiation, n (%)	
Well differentiated	26 (23.4)
Moderately differentiated	64 (57.7)
Poorly differentiated	21 (18.9)
Lymphatic invasion, present (%)	85 (76.6)
Venous invasion, present, (%)	50 (45.1)
Perineural invasion, present, (%)	104 (93.7)
Bile duct invasion, (%)	84 (75.7)

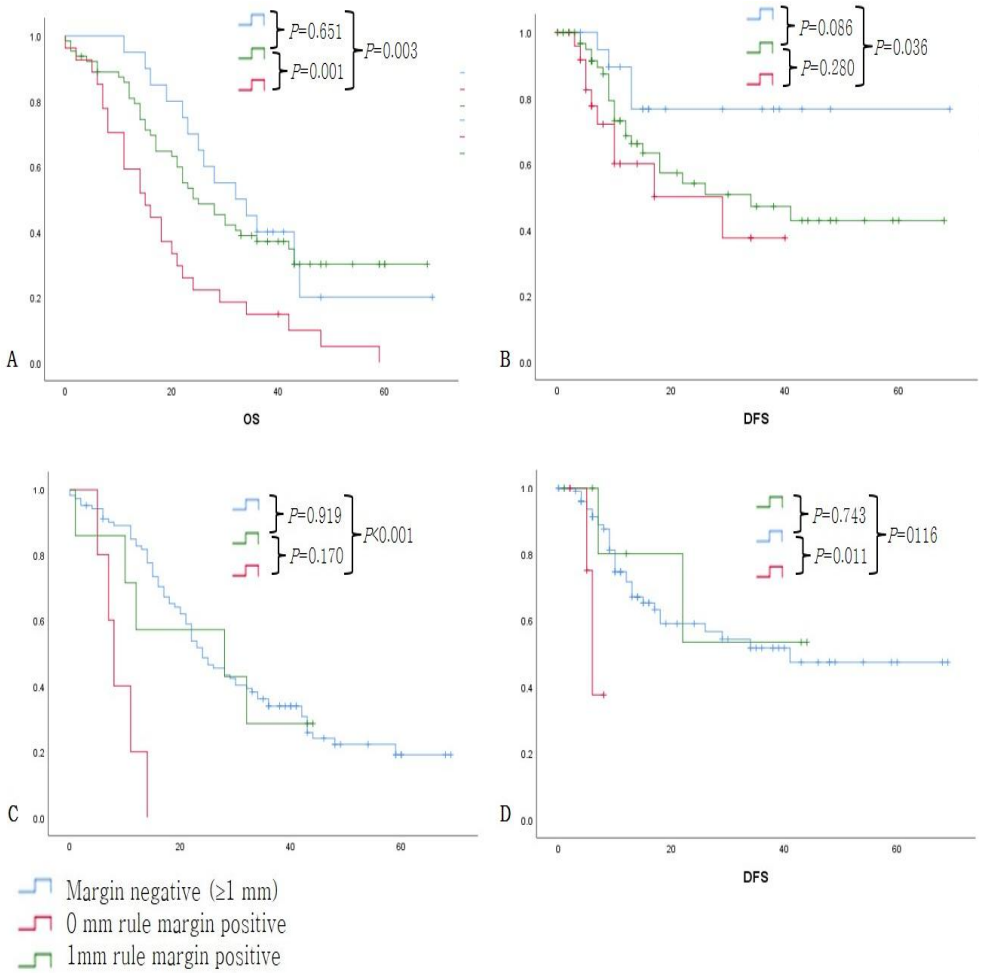
Duodenal invasion, (%)	59 (53.2)
pT stage, n (%)	
pT1	10 (9.0)
pT2	89 (80.1)
pT3	12 (10.9)
pT4	0 (0)
pN stage, n (%)	
pN0	25 (22.6)
pN1	47 (42.3)
pN2	39 (35.1)
Number of positive lymph nodes	3.1±3.2
Total number of lymph nodes	21.8±8.5
Resection margin/surface status (at least 1 positive margin), n (%)	
0 mm rule	26 (23.4)
1 mm rule	91 (82.0)
Adjuvant treatment, n (%)	90 (81.1)
Postoperative complications (Clavien − Dindo grade≥3a), n (%)	23 (20.7)

Survival outcomes according to the resection margin/surface status

The patients were followed up for a median of 29 months (range: 6 – 69 months). The median OS was 23 months (95% CI = 19.071–26.929), and the median DFS was 41 months (95% CI = 33.654–47.135). During the follow–up period, 82 patients died. Local recurrence and distant metastasis were observed in 33 (29.7%) and 56 (50.5%) patients, respectively.

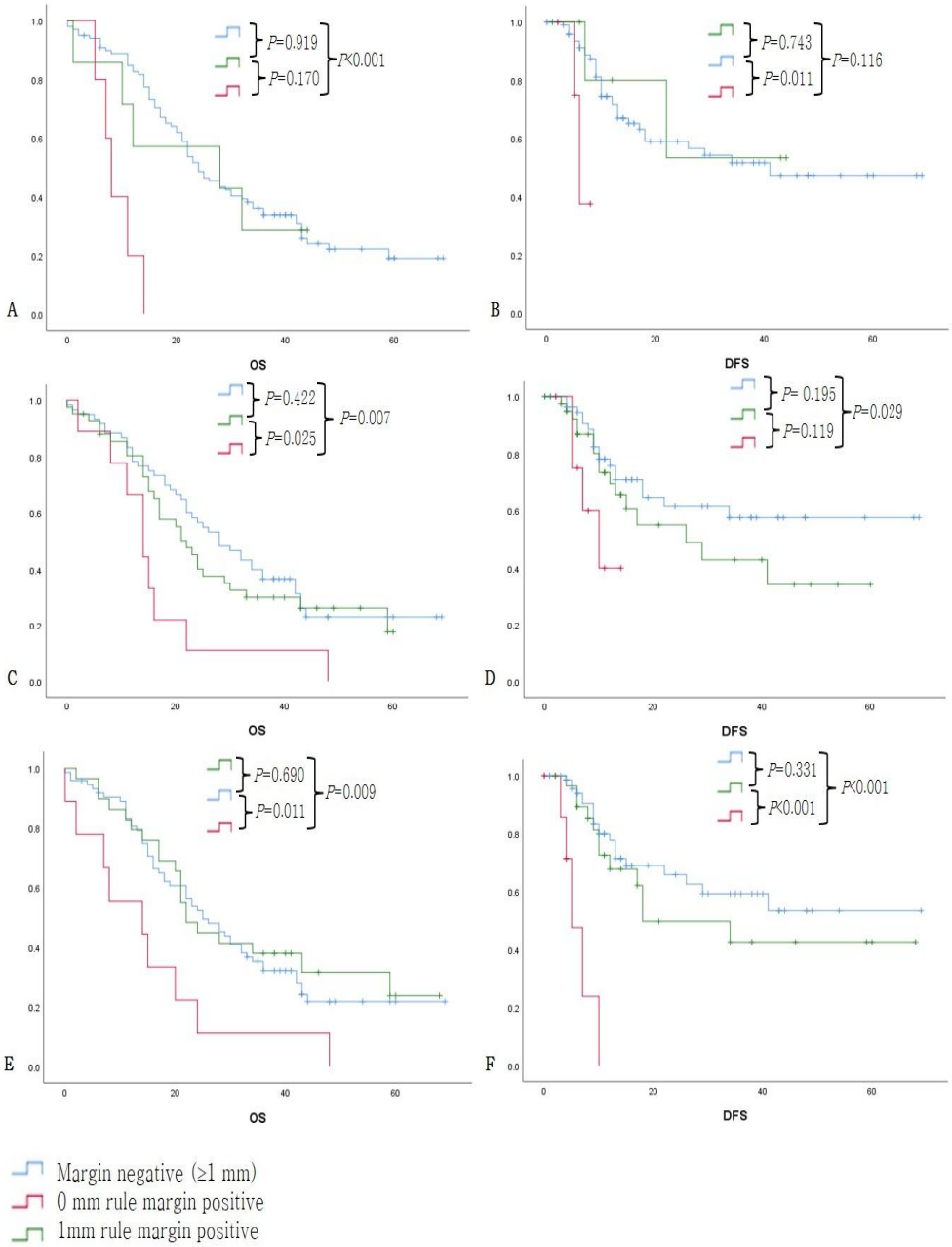
We analyzed the OS and DFS according to each margin/surface status (0 mm rule R1, 1 mm rule R1 and R0 [≥1 mm]). In the analysis of the overall resection margin, including the neck, SMV/PV and SMA margins, the 0 mm R1 had significantly lower rates of OS and DFS than those of 1 mm R1 and R0 (≥1 mm). There were no significant differences in OS and DFS between R0 (≥1 mm) and 1 mm R1. In the analysis of the overall surface, including the anterior and posterior surfaces, the R0 (≥1 mm) had a significantly higher OS rate than that of the 0 mm R1 and 1 mm R1, with no difference between the 0 mm R1 and 1 mm R1. However, there were no differences in DFS among the three groups (Figure 3). In the analysis of each margin status, the 0 mm R1 had significantly lower rates of OS and DFS than those of the 1 mm R1 and R0 (≥1 mm) without any difference between 1 mm R1 and R0 (≥1 mm) in the SMV/PV and SMA margins. There were differences in OS and DFS between 0 mm R1 and R0 (≥1 mm) in the neck margin (Figure 4). In the analysis of each surface, there were no differences in the OS and DFS in the anterior and posterior surfaces (Figure 5).

Figure 3. Survival analysis according to the resection margin/surface status



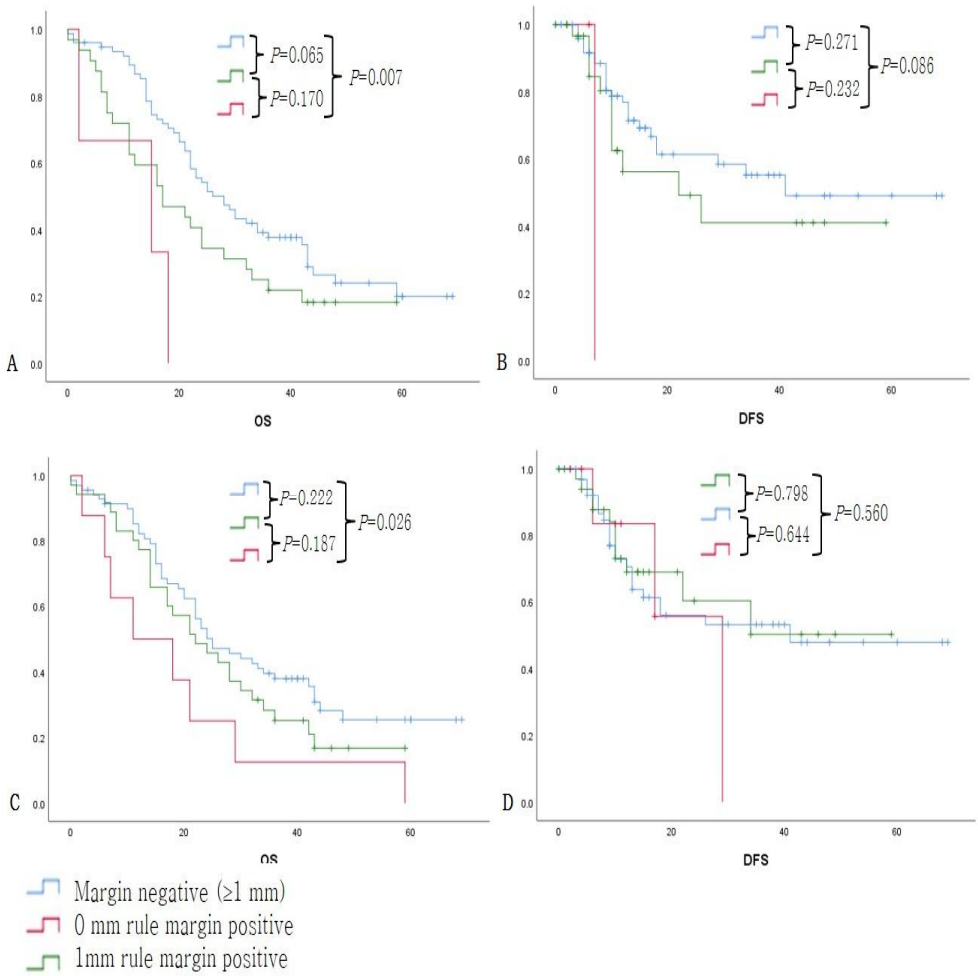
A. Overall survival (OS) in terms of the resection margin B. Disease-free survival (DFS) in terms of the margin C. OS in terms of surface D. DFS in terms of surface

Figure 4. Survival analysis according to each resection margin status



A. OS in the pancreatic neck margin B. Disease-free survival (DFS) in the pancreatic neck margin C. OS in the SMV/PV margin D. DFS in the SMV/PV margin E. OS in the SMA margin F. DFS in the SMA margin

Figure 5. Survival analysis according to each surface status



A. OS in the anterior surface B. Disease-free survival (DFS) in the anterior surface C. OS in the posterior surface D. DFS in the posterior surface

Prognostic risk factors for OS and DFS

In the multivariate analysis, female sex (p = 0.035, HR = 1.853, 95% CI = 1.043−3.291), histologic differentiation (moderate and poorly differentiated) (p = 0.004, HR = 3.061, 95% CI = 1.427−6.570), and 0 mm R1 in resection margin (p = 0.001, HR = 3.178, 95% CI = 1.628−6.203) were identified as independent risk factors for OS (Table 2). For DFS, only the 0 mm R1 in resection margin (p = 0.013, HR = 3.595, 95% CI = 1.308−9.885) was identified as an independent prognostic factor (Table 3). The surface margin by the 0 mm or 1 mm rule was not a significant risk factor for any survival outcomes.

Table 2. Prognostic risk factors for the overall survival

Variables	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*−value	HR (95% CI)	*P*−value
Age				
<70 years	Ref.	0.305		
≥70 years	1.289(0.793−2.095)			
Sex				
Male	Ref.		Ref.	
Female	0.617(0.386−0.987)	0.044	1.853(1.043−3.291)	0.035
Preoperative CEA				
<2 ng/ml	Ref.			
≥2 ng/ml	1.121(0.698−1.800)	0.637		
Preoperative CA19−9				
<100 u/ml	Ref.			
≥100 u/ml	1.443(0.889−2.344)	0.138		
ECOG				
0	Ref.			
1	1.409(0.701−2.834)	0.336		
ASA				
1,2	Ref.			
3	1.126(0.571−2.222)	0.732		
Combined VR				
No	Ref.			
Yes	1.196(0.745−1.921)	0.458		
Diagnosis				
IPMN	Ref.			
PDAC	3.013(0.939−9.661)	0.064		
Differentiation				
WD	Ref.		Ref.	
MD, PD	3.203(1.644−6.241)	0.001	3.061(1.427−6.570)	0.004
Lymphatic invasion				
No	Ref.			
Yes	1.925(0.909−4.073)	0.087		
Venous invasion				
No	Ref.		Ref.	
Yes	1.780(1.080−2.932)	0.024	1.515(0.850−2.701)	0.159
Perineural invasion				
No	Ref.			
Yes	0.657(0.121−3.561)	0.627		
Bile duct invasion				
No				
Yes	1.001(0.552−1.815)	0.997		
Duodenal invasion				
No	Ref.			
Yes	1.177(0.709−1.953)	0.529		
T stage				
T1	Ref.			
T2, 3	1.396(0.467−4.171)	0.550		
N stage				
N0	Ref.			
N1, 2	1.641(0.761−3.537)	0.206		
Adjuvant treatment				
No	Ref.		Ref.	
Yes	0.437(0.251−0.761)	0.003	0.516(0.255−1.045)	0.066
Postop Complication (Clavien−Dindo grade)				
<3a	Ref.		Ref.	
≥3a	2.755(1.576−4.815)	<0.001	1.105(0.584−2.088)	0.760

Surface				
0 mm rule				
R0	Ref.			
R1	1.575(0.773-3.210)	0.211		
1 mm rule				
R0	Ref		Ref.	
R1	2.030(1.226-3.361)	0.006	1.198(0.662-2.169)	0.121
Resection margin				
0 mm rule				
R0	Ref.		Ref.	
R1	4.090(2.218-7.544)	<0.001	3.178(1.628-6.203)	0.001
1 mm rule				
R0	Ref.		Ref.	
R1	0.703(0.409-1.209)	0.203	0.668(0.356-1.251)	0.207

Ref.: Reference, IPMN: Intraductal papillary mucinous neoplasm, PDAC: Pancreatic ductal adenocarcinoma, WD: Well-differentiated, MD: Moderately-differentiated, PD: Poorly differentiated

Table 3. Prognostic risk factors for the disease-free survival

Variables	Disease free survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age				
<70 years	Ref.			
≥70 years	1.140(0.555-2.342)	0.722		
Sex				
Male	Ref.			
Female	1.012(0.516-1.985)	0.971		
Preoperative CEA				
<2 ng/ml	Ref.			
≥2 ng/ml	0.777(0.403-1.501)	0.453		
Preoperative CA19-9				
<100 u/ml	Ref.			
≥100 u/ml	1.056(0.542-2.059)	0.872		
ECOG				
0	Ref.			
1	0.609(0.209-1.778)	0.364		
ASA				
1,2	Ref.			
3	1.151(0.434-3.052)	0.778		
Combined VR				
No	Ref.			
Yes	1.411(0.701-2.843)	0.335		
Diagnosis				
IPMN	Ref.			
PDAC	0.986(0.272-3.566)	0.986		
Differentiation				
WD	Ref.			
MD, PD	2.434(0.980-6.044)	0.055		
Lymphatic invasion				
No	Ref.			
Yes	1.687(0.641-4.436)	0.289		
Venous invasion				
No	Ref.			
Yes	1.245(0.578-2.681)	0.575		
Perineural invasion				
No	Ref.			
Yes	2.006(0.202-19.930)	0.552		
Bile duct invasion				
No	Ref.			
Yes	0.635(0.268-1.501)	0.301		
Duodenal invasion				
No	Ref.			
Yes	0.990(0.475-0.061)	0.978		
T stage				
T1	Ref.			
T2, 3	1.006(0.315-3.206)	0.993		
N stage				
N0	Ref.			
N1, 2	2.219(0.701-7.028)	0.175		
Adjuvant treatment				
No	Ref.			
Yes	1.238(0.455-3.367)	0.675		
Postop Complication (Clavien-Dindo grade)				
<3a	Ref.			
≥3a	1.894(0.858-4.182)	0.114		

Surface				
0 mm rule				
R0	Ref.			
R1	1.640(0.523−5.140)	0.396		
1 mm rule				
R0	Ref.			
R1	0.583(0.277−1.230)	0.157		
Resection margin				
0 mm rule				
R0	Ref.			
R1	4.559(1.890−10.998)	0.001	3.595(1.308−9.885)	0.013
1 mm rule				
R0	Ref.			
R1	2.360(0.991−5.622)	0.052		

Ref.: Reference, IPMN: Intraductal papillary mucinous neoplasm, PDAC: Pancreatic ductal adenocarcinoma, WD: Well−differentiated, MD: Moderately differentiated, PD: Poorly differentiated

Recurrence according to the resection margin/surface status

Of the 111 patients, 26 patients (23.4%) had R1 by the 0 mm rule while the R1 rate increased to 82.0% (91 of 111) by the 1 mm rule. When each circumferential margin/surface recurrence rate by the 0 mm and 1 mm-rules was analyzed, the anterior surface was involved in 3 (2.7%) and 35 (31.5%) cases; the posterior surface was involved in 8 (7.2%) and 43 (38.7%) cases; the SMV/PV groove margin was involved in 15 (13.5%) and 74 (66.7%); and the SMA margin was positive in 8 (7.2%) and 38 (34.2%) patients, respectively. The pancreatic neck margin was involved in 5 (4.5%) and 12 (10.8%) patients. The SMA margin involvement by the 0 mm rule was significantly associated with local recurrence after surgery (p = 0.036) with a marginal significance using the 1 mm rule (p = 0.052). Involvement of the other resection margin/surfaces using both 0 mm and 1 mm rules was not associated with local recurrence and distant metastasis (Table 4).

Table 4. Local recurrence and distant metastasis according to the resection margin/surface status

Margin /Surface	Margin rule	n (%)	Local recurrence (%) (R0 vs R1)	*P*-value	Distant metastasis (%) (R0 vs R1)	*P*-value
Margin	0 mm	17 (15.3)	26.6 vs 50.0	0.104	51.1 vs 50.2	0.938
	1 mm	75 (67.6)	16.7 vs 36.4	0.061	61.1 vs 46.0	0.138
Neck	0 mm	5 (4.5)	29.3 vs 40.0	0.611	50.0 vs 60.0	0.708
	1 mm	12 (10.8)	29.3 vs 33.3	0.775	50.5 vs 50.0	0.974
SMV/PV	0 mm	15 (13.5)	29.2 vs 33.3	0.745	47.9 vs 66.7	0.184
	1 mm	74 (66.7)	21.6 vs33.8	0.172	62.2 vs 44.6	0.082
SMA	0 mm	8 (7.2)	27.2 vs 62.5	0.036	51.5 vs 37.5	0.482
	1 mm	38 (34.2)	23.3 vs 42.1	0.052	49.3 vs 52.6	0.743
Surface	0 mm	10 (9.0)	29.0 vs 40.0	0.474	49.0 vs 70.0	0.218
	1 mm	57 (51.4)	32.1 vs 28.1	0.651	43.4 vs 57.9	0.131
Anterior	0 mm	3 (2.7)	29.6 vs 33.3	0.891	50.0 vs 66.7	0.668
	1 mm	35 (31.5)	27.6 vs 34.3	0.481	51.3 vs 48.6	0.790
Posterior	0 mm	8 (7.2)	29.1 vs 37.5	0.621	49.5 vs 62.5	0.513
	1 mm	43 (38.7)	29.4 vs 30.2	0.927	44.1 vs 60.5	0.095

2.3. Discussion

Hereby, we performed a prospective analysis of the clinicopathological and prognostic significance of circumferential margin involvement in PD specimens for PDAC. We aimed to evaluate the prognostic significance of the individual margin/surface of PD specimens and to compare the prognostic significance of margin/surface involvement using the 0 mm rule and the 1 mm rule.

In our study, the resection margin status using the 0 mm rule was more appropriate in estimating outcomes related to survival and recurrence than 1 mm rule. The 0 mm R1 had significantly lower rates of OS and DFS than 1 mm R1 and R0 (≥1 mm). In comparison, there were no significant differences in terms of OS and DFS between 1 mm R1 and R0 (≥1 mm) in all circumferential margin/surface. In the multivariate analysis of prognostic risk factors for OS and DFS, the R1 resection margin using the 0 mm rule was an independent risk factor for OS and DFS, while the surface status using the 0 mm/1 mm rules was not associated with OS and DFS. Especially the SMA margin was significantly associated with increased local recurrence.

In previous studies, the prognostic effect of resection margin/surface status in pancreatic head cancer has been controversial. Mois et al. (7), Kato et al., (8) and John et al. (9) reported that R1 resection using the 0 mm rule was not an independent risk factor for OS. In comparison, Winter et al. (10) and Chandrajit et al. (11) reported that the R1 resection using the 0 mm rule was an independent risk factor for OS. Crippa et al (12) reported that R1 resection in PDAC by 0 mm and 1 mm rules were independent risk factors of DFS.

Some previous studies estimated the circumferential

margin/surface status for prognosis of PDAC (Table 8). The R1 resection in the SMA margin using the 0 mm/1 mm rules was identified as an independent risk factor for OS in many studies (12–15). Some studies reported that the SMV/PV margin R1 resection by 1 mm rule was an independent risk factor for OS and DFS (10,15). In comparison, the prognostic effect of R1 resection in the posterior and anterior surfaces was controversial (11,15–17). The pancreatic neck margin R1 resection in 0 mm/ 1 mm rules was not associated with prognosis in most studies (11,14,16,17).

All studies regarding the circumferential margin/surface status in PD in Table 8 used the axial slicing technique to evaluate the surgical specimen. The axial slicing technique, also called the Leeds Pathology Protocol, is recommended by the Royal College of Pathologists. It was easy to reconstruct the pancreatic anatomy and to evaluate the circumferential margins using this method. It involves slicing the specimen perpendicular to the longitudinal axis of the duodenum, resulting in many thin slices in a single axial plane. The dissection plane was fixed, independent of the duct configuration and the key anatomic structures could therefore be easily identified. The specimen was first oriented, and the entire circumference of the pancreas was colored according to the preset ink codes. After fixation, the specimen was sliced axially, and the tumor size and the distance from all inked margin/surface were measured.

Our study has limitations, including a relatively small number of patients and a heterogenous follow–up period for recurrence and different adjuvant treatment protocols. These make it difficult to validate the independent prognostic effect of each circumferential margin/surface. To overcome these limitations, a well–designed,

large-scale study is needed in the near future. Despite these limitations, our study has strengths. We analyzed the OS and DFS according to both the 0 mm and 1 mm rules in all resection margins/surfaces of pancreatioduodenectomy using the axial slicing technique. Most of the previous studies on each resection margin/surface in the pancreatic head cancer analyzed resection margin/surface only by the 0 mm or 1 mm rules. We also analyzed the recurrence pattern, including the local recurrence and distant metastasis according to the circumferential margin/surface of pancreatic ductal adenocarcinomas.

Table 5. Previous studies on the prognostic significance of circumferential margin status in pancreatic ductal adenocarcinoma using the axial slicing technique

Author	Patients	Target margin	Conclusion
Luttges J et al. (13)	51	Retroperitoneal margin (SMA margin) in 0 mm rule	Risk factor for OS
Westgaard A et al. (14)	114	Retroperitoneal margin (SMA margin) in 0 mm rule	Risk factor for OS
Sabater L et al. (15)	100	Retroperitoneal margin (SMA margin) in 0 mm rule	Risk factor for OS
Crippa S et al. (12)	362	Circumferential margin/surface in 0 mm/ 1 mm rules	SMV margin R1 by 1 mm rule: risk factor for DFS Posterior surface R1 by 0 mm rule: risk factor for DFS
Zhang Y et al. (16)	258	Anterior and posterior surface status in 0 mm rule	Not association with DFS and OS
J.K. Pine et al. (17)	107	Circumferential margin/surface in 0 mm/1 mm rules	SMV and SMA margins R1 in 1 mm rule: risk factor of OS
Caitlin A et al. (18)	891	Circumferential margin/surface in 1 mm rules	Posterior surface R1 in 1 mm rule: risk factor of local recurrence

OS: Overall survival, DFS: Disease-free survival

Chapter 3. Conclusion

3.1. Conclusion

A "positive margin" by the 0 mm rule in resection margin was found to be an independent risk factor of OS and DFS. The R1 SMA margin was associated with increased risk of local recurrence rather than systemic recurrence. In comparison, a positive margin by the 1 mm rule was not associated with OS and DFS. These findings suggest that the 0 mm rule is more appropriate in predicting the recurrence and survival than 1 mm rule. To confirm our findings, a well-designed large-scale study is needed.

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국 문 초 록

배경: 현미경적 잔존암 (R1 절제)은 췌관선암 (PDAC)의 독립적인 예후 인자로 보고되었지만 췌관선암에 대한 R1 절제의 의미는 다음과 같은 이유로 다양하다. 1) R1 절제의 정의에 대한 합의 부족(1 mm 규칙 대 0 mm 규칙), 2) 다양한 절제 변연 및 표면(예: 전방, 후방, 상부 장간막 정맥/간문맥 (SMV/PV) 및 상부 장간막 동맥(SMA)), 및 3) 췌장 십이지장 절제술 표본에 대한 병리학 실험실의 다양한 육안적 병리 소견.

대상 및 방법: 2014년 3월부터 2018년 12월까지 분당서울대학교 병원에서 췌십이지장절제술과 혈관절제를 같이 시행한 경우(n=36) 또는 시행하지 않은 경우(n=75)의 췌관선암 111예를 대상으로 전향적 임상병리학적 분석을 시행하였다. 췌장의 모든 절제 변연 및 표면 (전방, 후방, SMV/PV, SMA, 췌장 경부), 담관 가장자리 및 십이지장 경계는 표준화된 잉크로 도색되었으며, 축 절단 방법으로 절단되었다. 전체 췌장 두부는 조직병리학적 매핑을 위해 수집 및 구분되었으며 모든 경계/표면에 대한 안전연은 밀리미터로 기록되었다. 환자들은 최대 69개월(중앙값: 23개월) 동안 추적 관찰되었으며, 절제 변연 및 표면 상태는 전체 생존(OS), 무병 생존(DFS), 무국소재발 생존(LRFS), 무원발전이 생존(DMFS) 및 수술 후 합병증을 포함한 환자 결과와 상관관계를 분석하였다. 절제 표면은 전방 표면, 후방 표면으로 정의하였고, 절제 변연은 췌장 경부 변연, SMV/PV 변연, SMA 변연으로 정의하였다.

결 과: 111개의 증례 중 26명/111명 (23.4%)의 경우가 0 mm 규칙에 의한 R1이었고 R1 비율은 1 mm 규칙에 의해 91명/111명 (82.0%)으로 증가하였다. 여성 [P=0.035, HR 1.853 (95% CI 1.043-3.291)], 세포 분화도 (중등도분화도, 저분화도) [P=0.004, HR 3.061 (95% CI 1.427-6.570)], and 0 mm 규칙에 의한 절제 변연 양성인 경우가 [P=0.001, HR 3.178 (95% CI 1.628-6.203)] OS의 독립 예후

인자였다. DFS의 경우, 0 mm 규칙에 의한 절제 변연이 포함된 경우 [P=0.013, HR 3.595 (95% CI 1.308-9.885)] 만이 독립 예후 인자였다. 0 mm, 1 mm 규칙으로 각 주변 절제 변연 및 표면별 재발율을 분석한 결과, 췌장 경부 변연 5명 (4.5%), 12명 (10.8%), 전방 표면 3명 (2.7%), 35명 (31.5%), 후방 표면 8명 (7.2%), 43명 (38.7%)였으며 SMV/PV 변연은 각각 15명 (13.5%)와 74명 (66.7%), SMA 변연은 각각 8명 (7.2%) 및 38명 (34.2%)에서 재발 소견을 보였다. SMA 변연 침범은 0 mm (*P*=0.036) 규칙에서 적용했을 때 수술 후 국소 재발과 유의한 관련이 있었다.

결 론: 절제연의 0 mm 규칙에 의한 '절제연 양성'은 OS와 DFS의 독립적인 위험 인자이며, SMA 변연 양성은 전신 재발이 아닌 국소 재발의 위험 증가와 관련이 있었다. 비교하면 1 mm 규칙에 의한 절제연 양성은 OS 및 DFS와 연관되지 않았다. 이러한 결과는 1 mm 규칙보다 0 mm 규칙이 재발과 생존 예측에 더 적합하다는 것을 시사한다. 위의 연구 결과를 검증하려면 적절하게 설계된 대규모 연구가 필요하다.

주요어: 췌장두부암, 절제연, 절제연 평가, 췌십이지장 절제술, 췌관선암
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