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Clinical significance of revised microscopic positive resection margin status in ductal adenocarcinoma of pancreatic head

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Purpose: Recent studies have suggested microscopic positive resection margin should be revised according to the presence of tumor cells within 1mm of the margin surface in resected specimens of pancreatic cancer. However, the clinical meaning of this revised margin status for R1 resection margin was not fully clarified.
Methods: From July 2012 to December 2014, the medical records of 194 consecutive patients who underwent pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head were analyzed retrospectively. They were divided into 3 groups on margin status; revised microscopic negative margin (rR0) – tumor exists more than 1 mm from surgical margin, revised microscopic positive margin (rR1) – tumor present within less than 1 mm from surgical margin, classic microscopic positive margin (cR1) – tumor is exposed to surgical margin.
Results: There were 76 rR0 (39.2%), 100 rR1 (51.5%), and 18 cR1 (9.3%). There was significant difference in disease-free survival rates between cR1 vs. rR1 (8.4 months vs. 24.0 months, P = 0.013). Margin status correlated with local recurrence rate (17.1% in rR0, 26.0% in rR1, and 44.4% in cR1, P = 0.048). There is significant difference in recurrence at tumor bed (11.8% in rR0 vs. 23.0 in rR1, P = 0.050). Of rR1, adjuvant treatment was found to be an independent risk factor for local recurrence (hazard ratio, 0.297; 95% confidence interval, 0.127–0.693, P = 0.005).
Conclusion: Revised R1 resection margin (rR1) affects recurrence at the tumor bed. Adjuvant treatment significantly reduced local recurrence of rR1. Accordingly, adjuvant chemoradiation for rR1 group should be taken into account.
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Key Words: Pancreatic ductal carcinoma, Margins of excision, Pancreaticoduodenectomy, Survival, Recurrence

INTRODUCTION

Pancreatic ductal adenocarcinoma is one of the most aggressive malignant diseases and usually shows poor prognosis [1]. Surgical resection remains the only potentially curative treatment but the survival rate of patients who undergo curative resection is only 15%–26% [1-6]. In several previous studies, the positive microscopic resection margin status was shown as an independent prognostic factor [7-10]. Many surgeons have tried to obtain a microscopic negative margin (R0) to improve the surgical outcome in this background. On the other hand, some recent studies demonstrated that resection margin status had no independent prognostic significance [1,11,12].

Furthermore, the deficiency of universally acceptable specimen handling and definition of R1 resection margin acts as an obstacle to research for improving the clinical outcome of resectable pancreatic cancer. Although the rate of R0 resections is regarded as a quality indicator after pancreatic cancer operation [13], a recent meta-analysis represented a wide range of R0 resection rates between 15% and 83% according to institutions [14]. In the early 2000s, the Royal College of Pathologists minimum dataset for histological reporting of Pancreaticoduodenectomy (PD) specimens recommends that cases with evidence of microscopic tumor extension to within 1 mm should be classified as R1 [15]. Since then, many studies have suggested the definition of microscopic positive margin be revised. However, the clinicopathologic meaning of this is still questionable.

We aimed to find out clinicopathologic details, risk factors for survival, and recurrence according to resection margin status, and finally to evaluate the effect of revised microscopic positive margin in which the tumor is within 1 mm from the margin surface to clinical outcome.

METHODS

The Institutional Review Board at Samsung Medical Center approved the exemption of this retrospective study and the approval number is 2016-10-086. Between July 2012 and December 2014, a total of 194 patients underwent PD due to ductal adenocarcinoma of the pancreatic head with curative intent in a single center. Clinicopathologic outcome data were prospectively collected in medical records and retrospectively reviewed. The patients consisted of 120 males and 74 females with a median age of 64.1 ± 10.1 years. One hundred forty-nine of 194 patients (76.8%) had adjuvant treatment after operation. Among them, 143 patients (96%) received concurrent chemoradiotherapy (CCRT), 5 patients (3.4%) received chemotherapy alone and only 1 case had radiotherapy alone. Gemcitabine-based chemotherapy was applied to 7 patients (4.9%), and the other 136 patients (95.1%) received 5-fluorouracil

(5-FU)-based chemotherapy. Among the 194 patients who underwent PD, no 30-day mortality occurred.

Specimens after operation were fixed in formalin overnight and the resection margin inked in 3 different colors according to 3 discrete regions: the superiors mesenteric artery (SMA) margin, the portal vein margin, and the pancreas neck margin. Then, specimens were sliced axially perpendicular to the longitudinal axis of the duodenum in a 4- to 5-mm thickness. Histopathologic examination was performed and microscopic safety margin was measured from invasive front of ductal adenocarcinoma to each inked margin with an ocular lens scale bar in the microscope (Fig. 1). All the histology reports were documented by one pathologist and evidence of tumor involvement at any one of these three margins was reported in an R1 classification. Patients were divided into 3 groups based on the margin status: rR0 (revised grossly and microscopically negative resection margin, microscopic safety margin >1 mm), tumor existing more than 1 mm from resection margin; rR1 (revised grossly negative but microscopically positive resection margin, 0 mm < microscopic safety margin ≤ 1 mm), tumor involved within 1 mm from each margin, but does not directly reach it; cR1 (classic microscopic positive resection margin, safety margin = 0 mm), tumor is exposed to inked microscopic margin. There were 76 rR0 (39.2%), 100 rR1 (51.5%), and 18 cR1 (9.3%).

Demographic and clinical features of all data except operation procedure, regional lymph node (LN) metastasis and
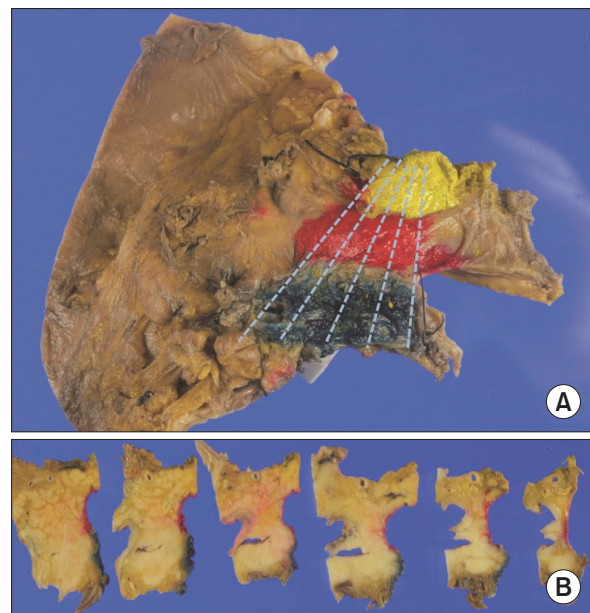

Fig. 1. Specimen handling after PD. (A) Fixed and inked specimen. The superior mesenteric artery margin (green), portal groove margin (red), and pancreatic neck margin (yellow) are identified. (B) Specimens were sliced axially in 4- to 5-mm thickness.

Table 1. Demographics, operation details, clinicopathologic features

Variable	rR0 (n = 76)	rR1 (n = 100)	cR1 (n = 18)	P-value
Age (yr)	64.4 ± 10.0	63.7 ± 10.6	61.8 ± 10.0	0.618
Sex, male:female	49:27 (65:35)	59:41 (59:41)	12:6 (69:31)	0.597
Body mass index (kg/m^2)	23.2 ± 3.2	22.4 ± 2.9	21.6 ± 2.9	0.095
ASA PS classification, I:II:≥III	10:66:0	12:86:0	3:15:0	0.589
Comorbidity	43 (56.6)	59 (59.0)	11 (61.1)	0.889
Cardiovascular disease	37 (48.7)	45 (45.0)	10 (55.5)	
Cerebrovascular disease	0 (0)	2 (2.0)	1 (5.5)	
Diabetes mellitus	27 (35.5)	44 (44.0)	6 (33.3)	
Pulmonary disease	3 (3.9)	14 (14.0)	0 (0)	
Preoperative CEA (ng/mL)	2.4 ± 1.9	2.6 ± 1.7	2.1 ± 1.3	0.680
Preoperative CA 19-9 (U/mL)	425.1 ± 1,234.2	622.1 ± 1,310.7	282.0 ± 322.1	0.532
Preoperative bilirubin (mg/dL)	4.2 ± 4.4	3.9 ± 4.4	3.8 ± 4.2	0.935
Operative methods, Whipple's OP:PPPD:PRPD	3:48:25 (63.1%)[a]	9:59:32 (59%)[a]	0:9:9 (50%)[a]	0.015
PV-SMV resection	14 (18.4)	32 (32.0)	5 (27.8)	0.127
Operation time (min)	339.2 ± 67.6	358.1 ± 79.8	361.6 ± 73.4	0.206
Blood loss (mL)	545.7 ± 699.4	598.0 ±561.8	532.1 ±323.5	0.814
Postoperative hospital stay (day)	12.3 ± 5.8	17.3 ± 40.0	12.9 ± 5.7	0.513
30-Day mortality	0 (0)	0 (0)	0 (0)	
Follow-up duration (mo)	17 (4–38)	15 (1–40)	15 (4–36)	0.298
Size of tumor (cm)	2.8 ± 1.0	2.9 ± 0.8	3.1 ± 0.9	0.411
T size				0.408
T ≥ 3 cm	32 (42.1)	49 (49.0)	11 (61.1)	
T < 3 cm	44 (57.9)	51 (51.0)	7 (38.9)	
Regional lymph node metastasis	43 (56.6)	77 (77.0)	17 (94.4)	0.002
Histologic grade				0.665
G1/G2	55 (72.4)	66 (66.0)	13 (72.2)	
G3/G4	21 (27.6)	34 (34.0)	5 (27.8)	
Perineural invasion	71 (93.4)	97 (97.0)	18 (100)	0.316
Lymphovascular invasion	45 (59.2)	78 (78.0)	14 (77.8)	0.018
Major vascular invasion[b]	13 (17.1)	28 (28.0)	5 (26.3)	0.231
Adjuvant treatment	62 (82.7)	70 (70.0)	17 (94.4)	0.091

Values are presented as mean ± standard deviation, number (%), or median (range).
rR0, microscopic safety margin >1 mm; rR1, 0 mm < microscopic safety margin ≤ 1 mm; cR1, safety margin = 0 mm; ASA PS, American Society of Anesthesiologists physical status; PPPD, pylorus preservingpancreaticoduodenctomy; PRPD, pylorus resecting pancreaticoduodenectomy; PV-SMV, portal vein-superior mesenteric vein.
[a]Proportion of number of patients receiving PPPD to all patients receiving curative resection. [b]Major vascular invasion means cancer invade to superior mesentery artery or portal vein or superior mesentery vein in final pathological findings.

lymphovascular invasion had no difference between the 3 groups (Table 1). However, more patients in the rR0 group had pylorus preserving pancreaticoduodenectomy operation compared to other operations including Whipple operation and pylorus resecting pancreaticoduodenectomy (63.1%, P = 0.015). We identified more regional LN metastases occurring in cR1 group (94.4%, P = 0.002) and higher rates of lymphovascular invasion in the rR1 group (78.0%, P = 0.018).

The follow-up schedule was determined by adjuvant treatment. For patients who needed adjuvant treatment, the follow-up interval was as follows: postoperative day (POD) 1 month, POD 2 months, POD 6 months, POD 12 months, POD 18 months, and every 6 months until POD 60 months after that. Regarding patients who needed no adjuvant treatment: at least 5 times for the first 18 months (POD 1, 4, 8, 12, 18 months) and every 6 months until POD 60 months after that. The routine follow-up examinations were composed of laboratory findings including tumor markers and image work up such as computed tomography. If no recurrence developed for 18 months after resection, the intervals of follow-up examinations were maintained up to 6 months. The median follow-up duration in the present study was 16.5 months (range, 1–40 months). We defined recurrence of disease according to radiologic or histologic findings. Local recurrence was defined as follows: if a local ill-defined mass or soft tissue or increase in size of LN along visceral vessels around the pancreatic bed were found by computed tomography evaluation with positive findings on positron-emission tomography. When it was combined distant

recurrence, we did not regard it as local recurrence.

Chi-square tests were used to cross-tabulate nominal data. Parametric continuous variables were tested using Student t-tests and the Mann-Whitney test was used for nonparametric continuous variables. The disease-free and overall survival rates were calculated using the Kaplan-Meier method and survival curves were compared using the log-rank test. Univariate survival and recurrence analysis to identify risk factors was conducted using the logistic regression model. Multivariate analysis was performed using Cox proportional hazards regression model. Statistical significance was set at a value of $P < 0.05$. We analyzed the data using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

Fig. 2A and B illustrates Kaplan-Meier cumulative curves of 3-year overall survival and disease-free survival rates according to microscopic resection margin status; rR0, rR1, and cR1. As shown in Fig. 2A, the rR1 group had a median survival of 22.3 months (95% confidence interval [CI], 19.5–25.4) compared with 24.7 months (95% CI, 21.6–27.3) for rR0 group ($P = 0.254$), and 17.0 months (95% CI, 12.5–21.6) for cR1 group ($P = 0.088$). With respect to disease-free survival rates, the median survival times were 16.0 months (95% CI, 13.0–18.9) in rR1 group, 17.1 months (95% CI, 13.8–20.3) in rR0 group ($P = 0.502$), and 8.4 months (95% CI, 4.6–12.2) in cR1 group ($P = 0.013$) (Fig. 2B).
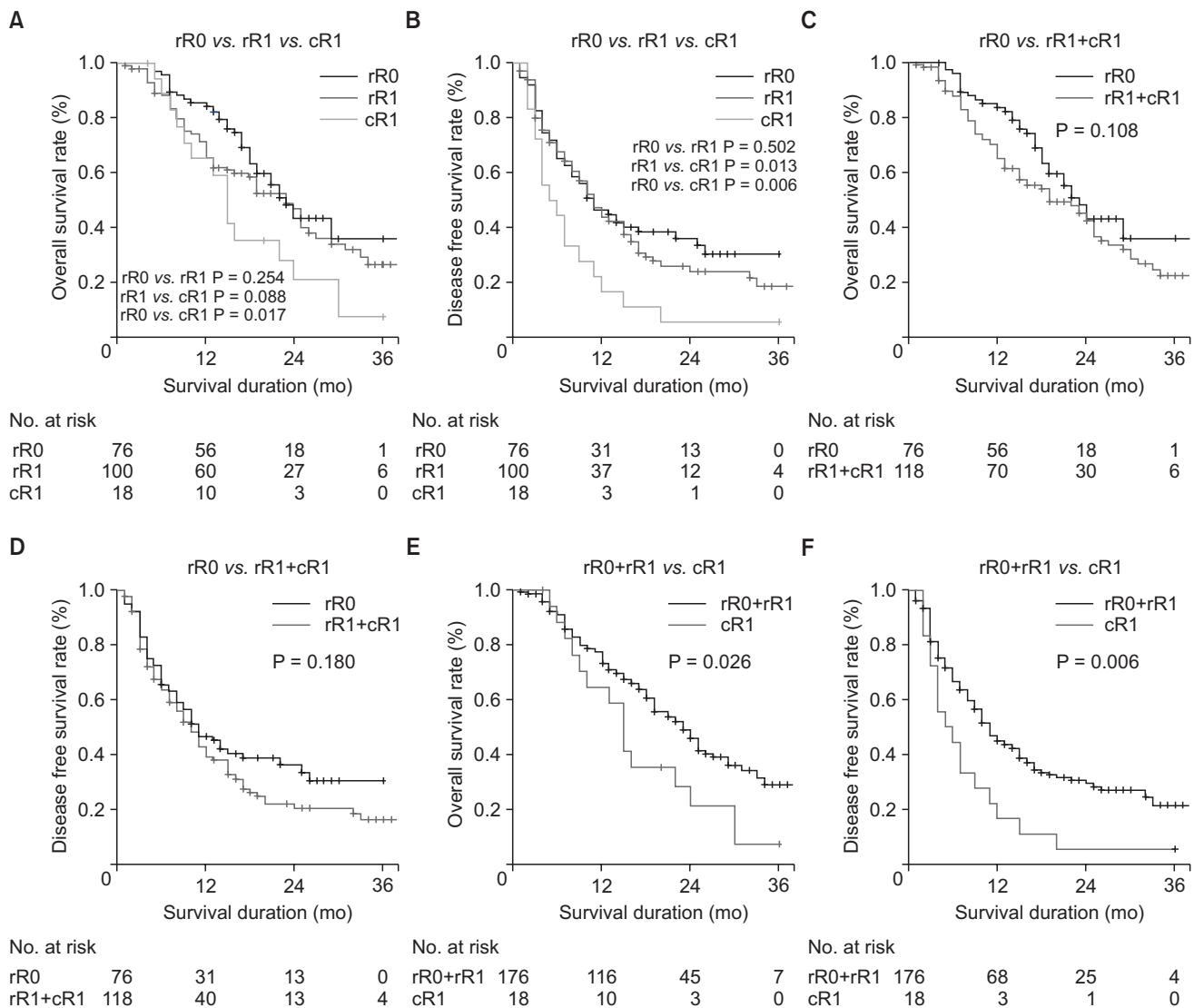

Fig. 2. Kaplan-Meier cumulative 3-year overall and disease-free survival curves according to microscopic resection margin status. Overall survival (A) and disease-free survival rates (B); rR0 *vs.* rR1 *vs.* cR1. Overall survival (C) and disease-free survival rates (D); rR0 *vs.* rR1 + cR1 under revised resection margin classification. Overall survival (E) and disease-free survival rates (F); rR0 + rR1 *vs.* cR1 under classic resection margin classification. rR0, microscopic safety margin >1 mm; rR1, 0 mm < microscopic safety margin ≤ 1 mm; cR1, safety margin = 0 mm.

When comparing the rR0 group versus rR1 + cR1 group (Fig. 2C, D) under revised resection margin classification, no significant difference in overall survival and disease-free survival rate was observed (24.7 months *vs.* 21.5 months, P = 0.108; 17.1 months *vs.* 14.7 months, P = 0.180). By contrast, we found significant differences in overall survival in comparison of rR0 + rR1 versus cR1 group under classic resection margin classification (23.7 months *vs.* 17.0 months, P = 0.026) (Fig. 2E). A significant difference in disease-free survival was also identified (16.7 *vs.* 8.4 months, P = 0.006) under classic resection margin classification (Fig. 2F).

Table 2 explains the results of both univariate and multivariate analysis of risk factors for survival. Multivariate analysis demonstrated that lower body mass index (hazard ratio [HR], 1.102; 95% CI, 1.039–1.207; P = 0.003), longer operation time (HR, 1.004; 95% CI, 1.001–1.007; P = 0.016), poorly differentiated histologic grade (HR, 2.622; 95% CI 1.713–4.013; P < 0.001), and cR1 microscopic resection margin (HR, 1.850; 95% CI, 1.076–3.179; P = 0.026) are significant prognostic factors for overall survival. As to recurrence, only poorly differentiated histologic grade (HR, 1.669; 95% CI, 1.153–2.416; P = 0.007) was a significantly independent risk factor for recurrence in multivariate analysis (Table 3).

The most common site of microscopic positive margin was portal vein-superior mesenteric vein (PV-SMV) margin. Of 100 rR1, PV-SMV (+) included 76 cases, SMA (+) 51 cases, and pancreas neck 3 cases. Of 18 cR1, PV-SMV (+) included 10 cases, SMA (+) 9 cases, and pancreas neck 2 cases.

Recurrence developed in 131 of 194 patients (67.5%) during the follow-up period of study. Among these, 91 patients (69.5%) received palliative chemotherapy and 40 patients (30.5%) had best supportive care. There was significant difference in recurrence rates between 3 groups; Recurrence rates were 63.2% (n = 48) in rR0 group, 66.0% (n = 66) in rR1 group, and 94.4% (n = 17) in cR1 group (P = 0.035). The correlation between the microscopic margin status and the initial recurrence sites was shown in Table 4. Local recurrence occurred in 13 of 76 patients (17.1%) in rR0 group, 26 of 100 patients (26.0%) in rR1 group, and 8 of 18 patients (44.4%) in cR1 group (P = 0.048).

We also analyzed recurrence patterns according to adjuvant treatment. Among the 45 patients (23.3%) who received no adjuvant treatment, there was significant difference in local recurrence rates; 7.1% (1 of 14) in rR0 group, 36.7% (11 of 30) in rR1 group, and 100.0% (1 of 1) in cR1 group (P = 0.028).

Table 2. Univariate and multivariate analysis of risk factor for survival

Characteristic	Univariate		P-value	Multivariate		P-value
	HR	95% CI		HR	95% CI	
Lower body mass index (<22.5 kg/m^2)	1.091	1.016–1.174	0.017	1.119	1.040–1.208	0.003
Longer operation time (>350 min)	1.004	1.001–1.007	0.010	1.004	1.001–1.007	0.016
Comorbidity	2.464	1.147–5.294	0.021	1.415	0.752–2.663	0.281
Larger size of tumor (>3 cm)	1.180	0.970–1.436	0.097	1.199	0.957–1.502	0.115
Poorly differentiated histologic grade	2.726	1.438–5.170	0.002	2.425	1.605–3.663	<0.001
Tumor presence of margin surface						
rR1 + cR1 *vs.* rR0	1.647	0.922–2941	0.092	1.066	0.677–1.679	0.783
cR1 *vs.* rR1 + rR0	5.581	1.571–19.836	0.008	1.850	1.076–3.179	0.026
Positive regional lymph node metastasis	1.873	1.005–3.490	0.048	1.185	0.750–1.873	0.466
Major vascular invasion	1.952	0.052–1.952	0.052	1.246	0.794–1.956	0.338

HR, hazard ratio; CI, confidence interval; rR0, microscopic safety margin >1 mm; rR1, 0 mm < microscopic safety margin ≤ 1 mm; cR1, safety margin = 0 mm.

Table 3. Univariate and multivariate analysis of risk factor for recurrence

Characteristic	Univariate		P-value	Multivariate		P-value
	HR	95% CI		HR	95% CI	
Longer operation time	1.002	1.000–1.005	0.084	1.002	0.999–1.005	0.144
Poorly differentiated histologic grade	2.462	1.135–5.338	0.023	1.669	1.153–2.416	0.007
Lymphovascular invasion	2.105	1.073–4.130	0.030	0.879	0.574–1.345	0.551
cR1 *vs.* rR1 + rR0	8.442	1.098–64.924	0.040	1.505	0.899–2.519	0.120
Adjuvant treatment	2.137	1.030–4.435	0.041	0.828	0.510–1.344	0.444

HR, hazard ratio; CI, confidence interval; rR0, microscopic safety margin >1 mm; rR1, 0 mm < microscopic safety margin ≤ 1 mm; cR1, safety margin = 0 mm.

Table 4. Correlation between microscopic margin status & initial recurrence site

Recurrence	rR0 (n = 76)	rR1 (n = 100)	cR1 (n = 18)	P-value
Recurrence rate	48 (63.2)	66 (66.0)	17 (94.4)	0.035
Locoregional recurrence	13 (17.1)	26 (26.0)	8 (44.4)	0.048
Tumor bed	9 (11.8)	23 (23.0)	7 (38.9)	0.021
Regional lymph node	4 (5.3)	4 (4.0)	2 (11.1)	0.326
Distant recurrence	34 (44.7)	47 (47.0)	12 (66.7)	0.237
Liver	26 (34.2)	28 (28.0)	7 (31.4)	0.527
Lung	7 (9.2)	13 (13.0)	4 (22.2)	0.309
Peritoneum	6 (7.9)	18 (18.0)	6 (33.3)	0.015

rR0, microscopic safety margin >1 mm; rR1, 0 mm < microscopic safety margin ≤ 1 mm; cR1, safety margin = 0 mm.

Regarding R0 versus rR1, no significant difference in total recurrence rates and local recurrence rates between rR0 and rR1 (63.2% *vs.* 66.0, P = 0.619; and 17.1% *vs.* 26.0%, P = 0.159) was found. However, there was significant difference in recurrence at tumor bed (11.8% *vs.* 23.0, P = 0.050). No significant difference in regional LN recurrence between the 2 groups was shown (5.3% *vs.* 4.0, P = 0.772). Among the rR1 groups, the 3-year cumulative local recurrence rate of patients receiving adjuvant treatment and no treatment was 35.5% and 66.3%, respectively (P = 0.034). Of rR1, adjuvant treatment and operation time were found to be independent risk factor for local recurrence by multivariable cox regression analysis (HR, 0.297; 95% CI, 0.127–0.693; P = 0.005 and HR, 1.010; 95% CI, 1.003–1.016; P = 0.002).

DISCUSSION

Recent studies demonstrated margin clearance as one of the most important prognostic factors in pancreatic cancer [7,9-11,14,16-19]. Esposito et al. [20] and Verbeke et al. [21] reported real R1 rates had been underestimated and insisted precise and standardized protocol should be used in specimen analysis in pancreatic cancer resection specimens. However, no universally accepted definition of resection margin for pancreatic cancer has existed to date. Chandrasegaram et al. [14] showed that R0/R1 rates vary according to different protocols of specimen processing and the R0 definitions used by each study in the first meta-analysis on this subject.

Furthermore, the concept of revised resection margin status is not validated internationally due to heterogeneity of different methods of neo or adjuvant treatment in each study and the absence of prospective studies. Application of the '1 mm rule' by the Leeds Pathology Protocol and the criteria of the British Royal College of Pathologists is mainly accepted in European countries. Whereas the '0-mm rule' as tumor cell at the surface of resection margin by the Union for International Cancer Control and American Joint Committee on Cancer criteria is used in United States [15,22,23]. Recently, the International

Study Group of Pancreatic Surgery strongly recommended the 1mm rule in evaluation of microscopic resection margin status [24]; however, more validation studies may be needed to confirm the clinical significance of the '1-mm rule' of revised resection margin status.

Several investigations showed revised R1 status is associated with poor prognosis compared to revised R0 status in multivariate analysis [9,16,17]. Two studies stratified the distance from resection margin by 0.5 mm and tried to determine a cutoff value for an optimal distance representing better long-term survival outcome [16,18]. As a result, it was concluded that security for clearance of more than 1.5 mm is an independent factor for long-term survival. In the study of Campbell et al. [7], the groups were divided in similar ways to our study: equivocal R1 (<1 mm), unequivocal R1 (direct), and R0 (≥1 mm). There was significant difference in overall survival between R0 and revised R1 groups but no difference between equivocal and unequivocal R1 resections. Strobel et al. [19] reported that margin status is a significant prognostic factor for survival irrespective of the resection margin status definition. However, we could identify the revised R1 group (tumor within 1 mm) represented by noticeable effects on median survival in this study.

By contrast, some studies raised questions about claims that the revised R1 system is significantly correlated with overall survival. There were no differences in disease-free survival and overall survival by Kaplan-Meier survival analysis between patients with $R_{>1\,mm}$ resection margin (microscopic safety margin >1 mm), $R_{0-1\,mm}$ resection margin and $R_{0\,mm}$ resection margin in investigation by Sugiura et al. [11] As in our investigation, a significant difference existed in rates of local recurrence according to 3 group of resection margin; 8% with $R_{>1\,mm}$, 20% with $R_{0-1\,mm}$, and 50% with $R_{0\,mm}$ patients (P < 0.001). However, there was no evidence of a direct relationship between local recurrence and distant recurrence in this study. Delpero et al. [25] used the '0-mm R1 rule' and represented patients with R1 (=0 mm) resection had a significantly poor outcome to those with R0 (>0 mm) in disease-free survival,

Although no difference was found in overall survival, they insisted on the validity of the '0-mm rule' within the framework of recurrence.

The issue of defining margin clearance is closely related to the way the tumor progresses. Considering that the growth pattern of pancreatic cancer is more sporadic and discontinuous than other cancers [26], the absence of tumor cells at the surface of the resection margin cannot be ruled out that no tumor cells remain in the organ. Therefore, the more sporadic the tumors are, the greater the distance they must acquire to achieve optimal clearance. In this regard, in the case of pancreatic cancer, it is reasonable to apply a "1-mm rule" to margin clearance for curative resection. Our study was conducted on the same lines as these previous studies. We attempted to directly compare revised resection margin classifications with the classic resection margin classifications. In the classic resection margin classification scheme (R>0 mm *vs.* R=0 mm), we could find significant differences in both overall survival rate and disease-free survival rate. Classic R1 margin status was a poor prognostic factor for survival in multivariate analysis. By contrast, there was no significant difference in both overall survival rate and disease-free survival rate in revised resection margin classification. No significant difference in overall survival between rR0 and rR1 existed like investigation by Sugiura et al. [11]. These results may seem to support the '0-mm rule' for resection margin in some ways. However, except in one study [11], all previous studies did not show sufficient data clarifying the relationship between resection margin and recurrence.

We found that revised R1 resection margin status, especially within 1-mm distance from the margin surface, can play a role as transitional zone by the result showing significant difference in recurrence at the tumor bed between rR0 and rR1. Actually, the local recurrence in the present study consists of recurrence at the tumor bed and regional LN involvement. We could identify that there is significant difference in recurrence at tumor bed (11.8% *vs.* 23.0, P = 0.050). However, no significant difference in regional LN recurrence between the 2 groups was shown (5.3% *vs.* 4.0, P = 0.772). Perhaps the statistical results of LN involvement seem to have affected no significant difference in the overall local recurrence. Of rR1 groups, significant difference in 3-year cumulative local recurrence rate according to adjuvant treatment was identified (no adjuvant

treatment – 66.3% *vs.* adjuvant treatment – 35.5%, P = 0.034). Between the 2 groups, there was no significant difference in cell differentiation, T stage, N stage, perineural invasion, and lymphovascular invasion. Furthermore, of rR1, adjuvant treatment was found to be an independent risk factor for local recurrence. As noted in the methods section, the proportion of CCRT was 96% of all adjuvant treatment. These results support the claim that adjuvant chemoradiation for the rR1 group may reduce local recurrence.

Whether local recurrence can be the main cause of death in pancreatic cancer is uncertain yet. Despite local recurrence being reported to happen frequently from an autopsy study in patients with curative resection, only 4 patients died of local recurrence in one study [27]. So, further investigation is needed to clarify a direct relationship between local recurrence after revised R1 resection and mortality.

Our study has some limitations. First, our institution had no standardized neoadjuvant or adjuvant protocol, and change of regimen in accordance with passage of time might have influenced the clinical outcome of patients. Most patients received 5-FU-based chemotherapy in this study because of the lower health insurance coverage on gemcitabine in Korea, and it may have caused selection bias. Second, the median follow-up time in our investigation was 16.5 months and we analyzed 3-year survival outcome. Thus, our studies may not reflect long-term clinical outcomes as compared to previous studies. The study design requires more future long-term, follow-up, and nationwide investigation.

In conclusion, we found that poorly differentiated histologic grade was a risk factor for recurrence in multivariate analysis. rR1 resection margin status significantly affects recurrence at the tumor bed. Of rR1, adjuvant treatment was found to be an independent risk factor for local recurrence. Thus, adjuvant local control such as chemoradiation for rR1 group should be taken into account. More studies will be needed to figure out the clinical significance of revised microscopic positive resection margin (rR1) in terms of local recurrence and survival analysis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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