



ORIGINAL ARTICLE

Clinical impact of margin status on survival and recurrence pattern after curative-intent surgery for pancreatic cancer



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KEYWORDS

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Surgical margin status

Summary *Background/Objective:* The definition of R0 resection for invasive pancreatic ductal carcinoma (IPDC) is important. However, there are different definitions among several countries in the world.

Methods: From 2001 to 2015, 100 consecutive patients with IPDC who underwent pancreatic resection in our hospital were enrolled. We compared survival and recurrence patterns between the R0 group and R1 group based on the UICC (Union for International Cancer Control) classification (current-R0 vs. current-R1) and based on our revised classification, which defines R0 as a surgical margin of >1 mm (revised-R0 vs. revised-R1).

Results: The 100 patients comprised 58 males and 42 females, and their median age was 70 [32–87]. There were 84 patients in the current-R0 group and 43 in the revised-R0 group. There was no difference in overall survival (OS) or recurrence-free survival (RFS) between the current-R0 group and current-R1 group. However, there was a tendency toward a higher OS rate in the revised-R0 than revised-R1 group (log-rank $p = 0.065$), and RFS was significantly better in the revised-R0 than revised-R1 group (log-rank $p = 0.002$). There was no significant difference in the recurrence patterns between the current-R0 and current-R1 groups. In contrast, the local recurrence rate was significantly lower in the revised-R0 than revised-R1 group (21% vs. 42%, respectively; $p = 0.026$).

Conclusion: The revised classification of surgical resection may be more useful than the current UICC classification for prediction of prognosis and local recurrence of IPDC.

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1. Introduction

The prognosis of invasive pancreatic ductal carcinoma (IPDC) is quite poor, with a 5-year survival rate of only 6%.¹ Only 10%–20% of patients with pancreatic cancer are candidates for surgical resection according to previous reports.^{2,3} In 1984, the 5-year survival rate after surgery was reportedly only 3%; however, the patient prognosis has been improving, and the 5-year survival rate after surgery was reportedly about 11%–25% during the last decade.^{4–7} This improvement may be attributable to the increased experience of surgeons performing pancreatic resection and possibly to the effects of adjuvant chemotherapy.

It is important to identify the clinical and pathological factors that affect the prognosis and that indicate the potential for invasion or metastasis of IPDC. Knowledge of these factors can help in the selection of patients who should receive adjuvant chemotherapy or other meticulous postoperative treatments to prevent recurrence. The prognostic factors after resection of IPDC have been analyzed in several reports. In particular, it is important to achieve a pathologically negative surgical margin status to ensure a greater chance of long-term survival.^{7–10} The distance of the resection margin has recently been studied with respect to its role in improved survival after resection of IPDC. Some reports have indicated that a resection margin of >1 mm yields a survival benefit, and others have reported that a margin of >1.5 mm is necessary for longer survival after resection. However, the distance of the resection margin required for prevention of recurrence and longer survival remains controversial.^{11–13}

In the present study, we focused on the distance of the surgical margin and evaluated the influence of the surgical margin on survival and recurrence patterns of patients with IPDC.

2. Methods

2.1. Patients

We enrolled 100 consecutive patients with IPDC who underwent pancreatic resection in our hospital during a 15-year period (2001–2015). First, the patients were classified into current-R0 and current-R1 groups based on the current classification of the surgical margin status as determined by the Union for International Cancer Control (UICC).¹⁴ This classification was performed for all 100 patients enrolled based on the newest UICC criteria in the 8th edition of the TNM classification edited by the International Union Against Cancer. Overall survival (OS), recurrence-free survival (RFS), and clinicopathological characteristics, including the recurrence patterns, were then compared between the groups. Second, the patients were classified into revised-R0 and revised-R1 groups based on our revised classification of the surgical margin status, in which revised-R0 is defined as a surgical margin of >1 mm. The same comparisons were then performed between the groups. As subgroup analyses, the same survival analyses were performed for patients who underwent pancreaticoduodenectomy (PD) and for patients who underwent distal pancreatectomy (DP).

Current-R0 was defined as no evidence of tumor cells at any of the resection margins on pathological examination of the resected specimen. Revised-R0 was defined as any resection margin of >1 mm. OS was measured from the date of the operation until the date of death or last follow-up, and RFS was measured until the date of recurrence. Recurrence was diagnosed by tumor markers and computed tomography; if necessary, magnetic resonance imaging, positron emission tomography, or biopsy with endoscopic ultrasound was added.

The present study was performed in compliance with the declaration of Helsinki and ethical principles for medical research involving human subjects. Informed consent was obtained from all patients enrolled in this study for the experimental use of their specimens.

2.2. Operative procedure

Fifty-eight patients underwent PD, 37 underwent DP, and 5 underwent total pancreatectomy (TP). Portal vein resection and reconstruction was performed in 29 patients. All pancreatectomies were performed with curative intent by hepatobiliary pancreatic surgeons in our hospital using a standardized procedure. D2 lymphadenectomy was performed based on the classification of the Japan Pancreas Society. For the retroperitoneal space, because we had already standardized the operative procedure, the anterior wall of the inferior vena cava was principally exposed in all operations, and Gerota's fascia was partially resected according to the degree of tumor invasion or specific operational method used. All operative procedures including the resected area were supervised by the director of our department (a board-certified hepatobiliary-pancreatic surgeon) for all patients enrolled in the present study.

Intraoperative pathological examination of the resection margin in the area of the main pancreatic duct was performed for 70 patients whose resection line was near the tumor; if necessary, additional resection was performed until a negative surgical margin was confirmed.

2.3. Statistical analysis

Data are presented as median and range. The log-rank test was used for the OS and RFS rates, and the χ^2 and Mann–Whitney tests were used for comparisons between the 2 groups. All reported p values are 2-sided. A p value of <0.05 was considered statistically significant. All statistical analyses were conducted using JMP, Version 10 (SAS Institute Inc., Cary, NC, USA) and reviewed by the chief statistician in our institution.

3. Results

In total, 100 patients were enrolled. The median observation period was 607 days. Table 1 shows the clinicopathological characteristics of all patients (58 males and 42 females with a median age of 70 [32–87] years at the time of pancreatic resection). Following the UICC criteria, the patients were staged according to their pathological status as follows: IA, n = 5; IB, n = 3; IIA, n = 38; IIB, n = 52; III,

Table 1 Clinicopathological characteristics of all patients.

Variables	Value (n = 100)
Age (years)	70 [32–87]
Gender	
Male/Female	58/42
Operative procedures	
Pancreaticoduodenectomy	58
Distal pancreatectomy	37
Total pancreatectomy	5
Tumor size (mm)	26 [5–80]
UICC T classification	
T1/T2/T3/T4	6/4/89/1
Lymph node metastasis	
Negative/Positive	47/53
UICC stage	
IA	5
IB	3
IIA	38
IIB	52
III	1
IV	1
Extrapancreatic neural plexus invasion	22
Portal invasion	29
Surgical margin status	
current-R0/current-R1	84/16
revised-R0/revised-R1	43/57
Adjuvant chemotherapy	64
Recurrence pattern	
Liver metastasis	30
Peritoneal dissemination	22
Local recurrence	33
Lymph node metastasis	8

Data are presented as median [range] or n. current-R, surgical margin status based on UICC classification; revised-R, surgical margin status based on our revised definition of R0 as a surgical margin of >1 mm.

n = 1; and IV, n = 1. Current-R0 was achieved in 84 patients and revised-R0 in 43 patients.

Fig. 1 shows the OS and RFS rates of all patients. The 1-, 3-, and 5-year OS rates were 79.7%, 40.9%, and 22.6%, respectively, and the 1-, 3-, and 5-year RFS rates were 54.2%, 22.2%, and 17.7%, respectively. Fig. 2 compares the

OS and RFS between the current-R0 group and current-R1 group and between the revised-R0 group and revised R1 group. There was no significant difference in OS or RFS between the current-R0 and current-R1 groups (log-rank $p = 0.245$ and 0.135 , respectively). However, there was a tendency toward a higher OS rate in the revised-R0 than revised-R1 group (log-rank $p = 0.065$), and RFS was significantly better in the revised-R0 than revised-R1 group (log-rank $p = 0.002$).

The results of the subgroup analyses based on the different operative procedures are shown in Figs. 3 and 4. Within the PD group, as shown in Fig. 3, RFS was significantly better in the revised-R0 than revised-R1 group (log-rank $p = 0.003$), while this difference was not seen between the current-R0 and current-R1 groups (log-rank $p = 0.222$). Within the DP group, as shown in Fig. 4, RFS tended to be better in the revised-R0 than revised-R1 group (log-rank $p = 0.155$), while this difference was not seen between the current-R0 and current-R1 groups (log-rank $p = 0.576$).

Table 2 compares the preoperative and clinicopathological characteristics between the current-R0 and current-R1 groups and between the revised-R0 and revised R1 groups. Only the revised classification showed significant differences in the rate of lymph node metastasis and the rates of intrapancreatic lymphatic, venous, and perineural invasion between the revised-R0 and revised-R1 groups. There was no significant difference in the recurrence patterns between the current-R0 and current-R1 groups. In contrast, the local recurrence rate was significantly lower in the revised-R0 than revised-R1 group (21% vs. 42%, respectively; $p = 0.026$).

4. Discussion

Many previous reports have indicated that R0 resection (pathologically complete resection of the tumor with a negative resection margin) is an important prognostic factor after resection of pancreatic cancer. In surgery for pancreatic cancer, R0 resection is generally reported to be achieved in 70%–80% of cases, but the definition of R0 resection is not standardized. Although a 0-mm resection margin has been adopted in Japan as the definition of R0 resection according to the Japan Pancreas Society classification, a minimum 1-mm margin has been adopted in many institutions in Europe. In several reports, the R0 resection

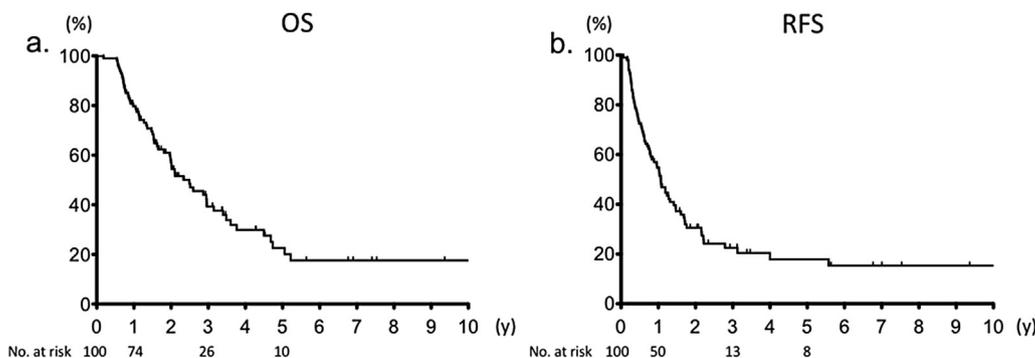


Figure 1 Overall survival (OS) and recurrence-free survival (RFS) of all 100 study patients. a. OS. b. RFS.

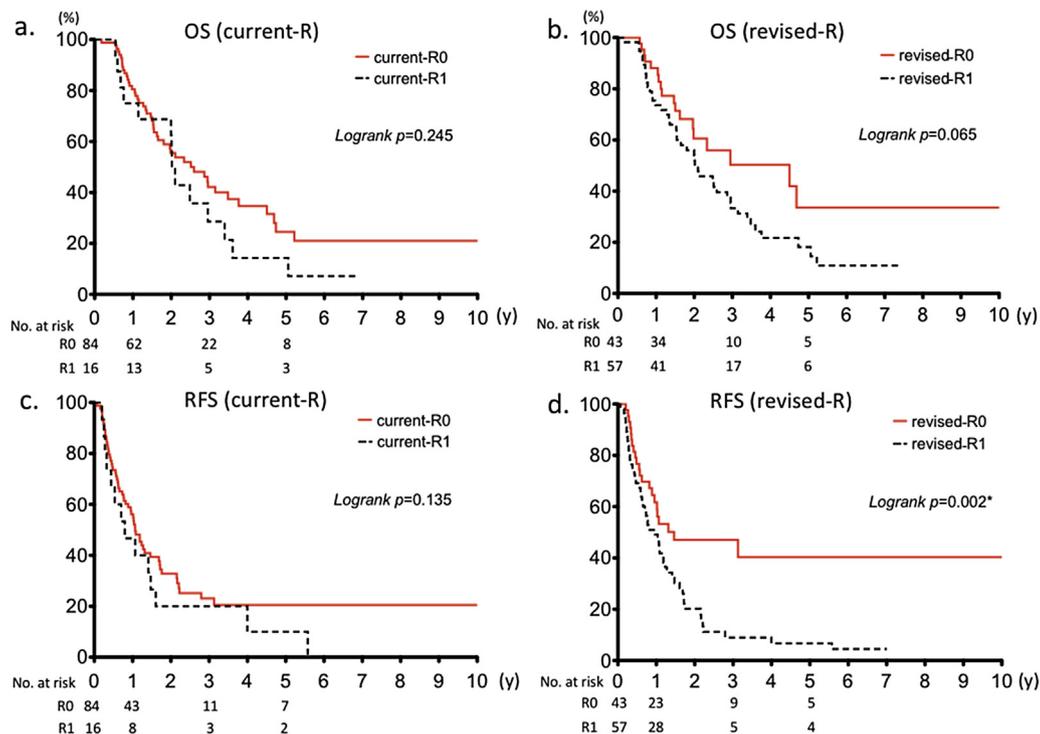


Figure 2 Comparison of overall survival (OS) and recurrence-free survival (RFS). a. Comparison of OS between current-R0 group and current-R1 group. There was no significant difference between the two groups (log-rank $p = 0.245$). b. Comparison of OS between revised-R0 group and revised-R1 group. There was a tendency toward a higher OS rate in the revised-R0 than revised-R1 group (log-rank $p = 0.065$). c. Comparison of RFS between current-R0 group and current-R1 group. There was no significant difference between the two groups (log-rank $p = 0.135$). d. Comparison of RFS between revised-R0 group and revised-R1 group. RFS was significantly better in the revised-R0 than revised-R1 group ($p = 0.002$).

rate was as low as 15%–26% when 1-mm margin was used to define R0 resection.^{15–19} Chandrasegaram et al performed a meta-analysis and found that the rate of R0 resection with a 0-mm margin was 72%, while that with a 1-mm margin was 41%.²⁰ Furthermore, Delpero et al performed a detailed analysis of margin distances and reported that the proportions of patients with resection margin distances of 0.0, <1.0, <1.5, and <2.0 mm were 23%, 61%, 63%, and 71%, respectively.²¹ Standardization of the definition of R0 resection is essential to ensure better prognostic analysis and patient selection for postoperative treatment.

The International Study Group of Pancreatic Surgery has suggested a 1-mm resection margin for borderline resectable tumors.²² However, there is insufficient evidence that a 1-mm resection margin ensures longer survival in patients with all types of pancreatic cancer. Few studies have analyzed the survival benefit of a 1-mm resection margin in patients with IPDC. Konstantinidis et al analyzed the clinicopathological factors from a pancreatic cancer database and reported that survival after resection with a ≤ 1 -mm margin was similar to that after R1 resection (positive surgical margin), and both groups had a significantly shorter median survival than patients with a margin of > 1 mm.¹¹ Chang et al analyzed 365 patients and reported that patients with a resection margin of > 1.5 mm had longer survival than those with a margin of ≤ 1.5 mm.¹³ We consider that it is important to identify the relationship between survival and the distance of the resection margin.

In the present study, we defined current-R0 resection as a resection margin of 0 mm and revised-R0 resection as a margin of > 1 mm. Current-R0 was achieved in 84% of patients, but revised-R0 was achieved in only 43%. We also compared survival between the current-R0 and current-R1 groups and between the revised-R0 and revised-R1 groups. We found no significant difference in OS or RFS between the current-R0 and current-R1 groups; however, there was a significant difference in RFS and the same tendency in OS between the revised-R0 and revised-R1 groups. The same tendency was also seen in the subgroup analyses based on the different operative procedures (PD and DP). Furthermore, significant differences in pathological characteristics such as intrapancreatic lymphatic, venous, and perineural invasion were present between the revised-R0 and revised-R1 groups, but not between the current-R0 and current-R1 groups. With respect to the rate of the recurrence patterns, the local recurrence rate was significantly higher in the revised-R1 than revised-R0 group. These results may indicate that revised-R0 resection (pathological 1-mm margin resection) is difficult to perform for tumors with highly invasive potential. This is compatible with the fact that the local recurrence rate was higher in the revised-R1 than revised-R0 group. Although little has been reported about the relationship between the margin status and pathological characteristics or recurrence patterns, Sugiura et al reported the same result regarding the margin status and recurrence

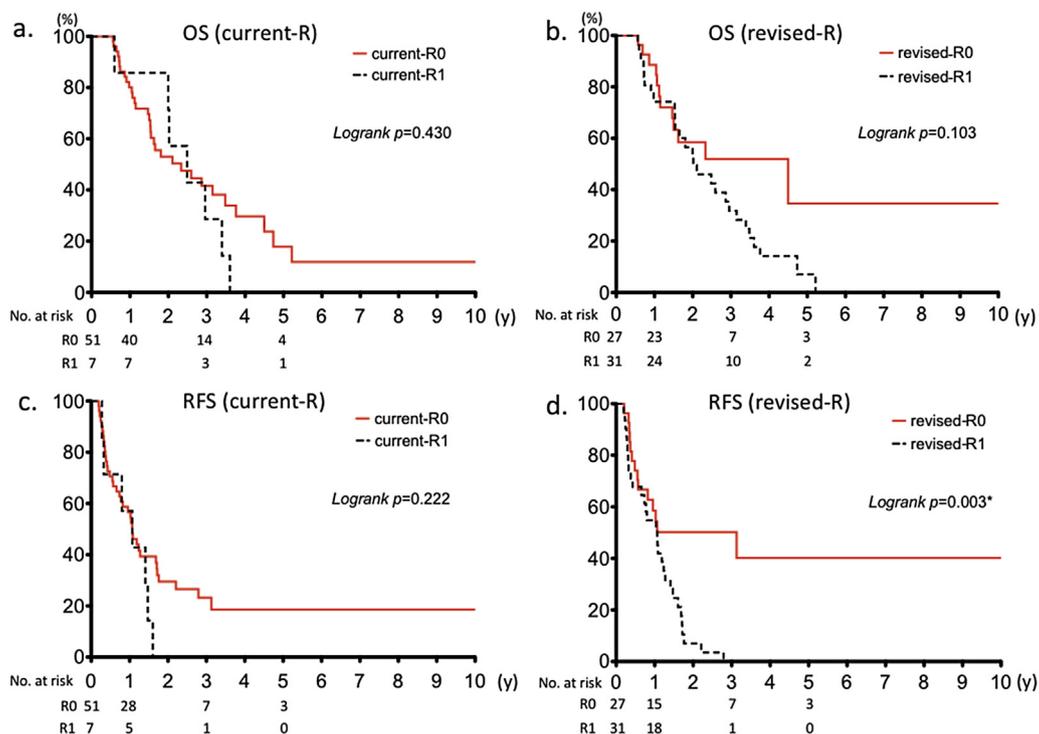


Figure 3 Comparison of overall survival (OS) and recurrence-free survival (RFS) within the PD (pancreaticoduodenectomy) group. a. Comparison of OS between current-R0 group and current-R1 group. b. Comparison of OS between revised-R0 group and revised-R1 group. c. Comparison of RFS between current-R0 group and current-R1 group. d. Comparison of RFS between revised-R0 group and revised-R1 group. RFS was significantly better in the revised-R0 than revised-R1 group (log-rank $p = 0.003$), while this difference was not seen between the current-R0 and current-R1 groups (log-rank $p = 0.222$).

patterns; that is, they found that the margin status was correlated with only the rate of local recurrence and not with the rate of other recurrence patterns.²³ Thus, our results show that revised-R0 is more closely associated with survival and could be a more useful predictor of the invasive potential of IPDC than current-R0. Furthermore, this may mean that for patients with current-R0 but not revised-R0, meticulous postoperative management or adjuvant treatment is definitely required due to the invasive potential of the tumor. In the present study, there was no significant difference in the rate of patients who received adjuvant chemotherapy between the current-R0 and current-R1 groups or between the revised-R0 and revised-R1 groups. In fact, as several patients did not receive adjuvant chemotherapy, especially in the early period, evaluation of the efficacy of adjuvant chemotherapy is quite difficult in this clinical setting. Therefore, the types of postoperative treatments needed for patients with revised-R1 resection also should be assessed in a larger study involving more patients.

Several previous studies have analyzed in detail the anatomical sites at which the resection margin was involved. For example, Delpero et al analyzed 3 resection margins that were multicenter-linked by the surgeons (portal vein–superior mesenteric vein margin, superior mesenteric artery margin, and posterior margin) in 150 specimens and reported that the most frequently involved resection margin (0-mm positive margin) was the portal vein–superior mesenteric vein margin (35% of study patients).²¹ In contrast, Esposito et al focused on the circumferential soft

tissue margins (medial, anterior surface, superior, and posterior) among 111 patients; they reported that the medial (68%) and posterior (47%) margins were most commonly involved and that in 32% of the patients, more than one margin was affected.¹⁶ These detailed analyses of the surgical margin status have led to improvements in surgical techniques required for resection with negative surgical margins and could improve survival. In the present retrospective study, there was insufficient data regarding the locations of surgical margin invasion. More detailed studies on the surgical margin status are essential in the future.

One of the strategies with which to increase the R0 resection rate is preoperative therapy. Some recent studies have reported the importance of preoperative therapy not only for initially unresectable or borderline resectable pancreatic cancer but also for resectable pancreatic cancer.^{24–26} Chun et al reported that the pathologic response to neoadjuvant chemoradiation therapy was associated with the R0 resection rate and survival.²⁵ In the present study, only 13 patients (13%) underwent preoperative treatment. Among them, 7 patients underwent neoadjuvant chemoradiation therapy, and the other 6 patients received neoadjuvant chemotherapy. Although the difference was not significant, the rate of R0 resection was higher in patients with than without preoperative treatment in both the current and revised classifications. To assess the benefit of preoperative therapy on the R0 rate, more patients who underwent preoperative therapy should be evaluated in such studies in the future.

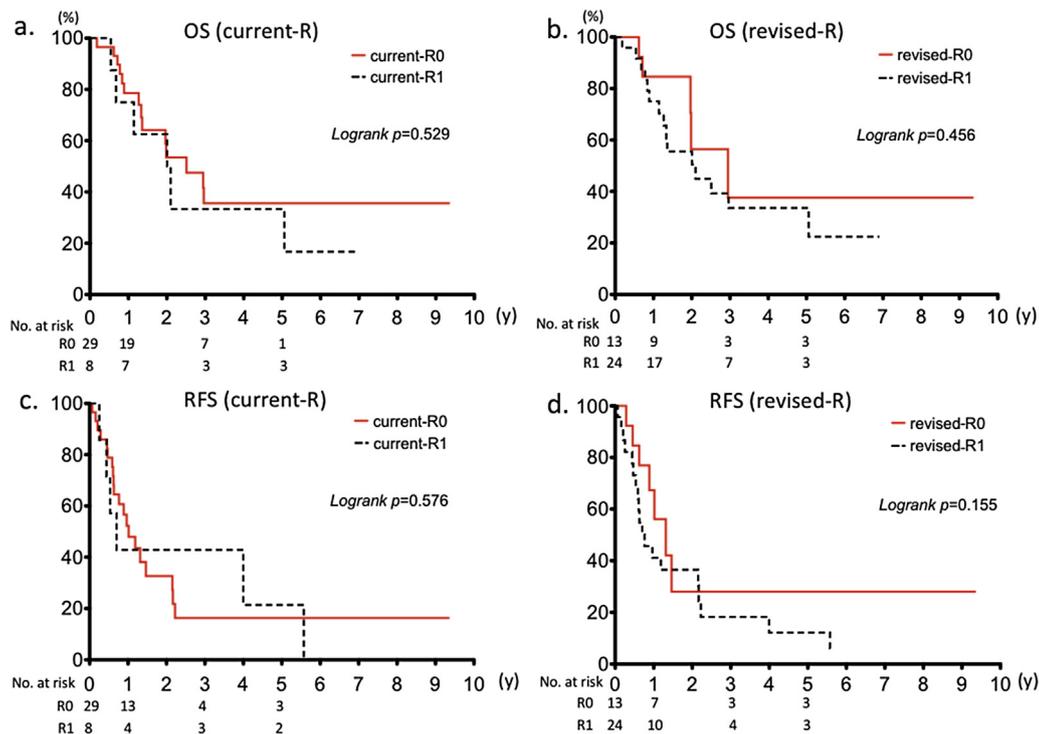


Figure 4 Comparison of overall survival (OS) and recurrence-free survival (RFS) within the DP (distal pancreatectomy) group. **a.** Comparison of OS between current-R0 group and current-R1 group. **b.** Comparison of OS between revised-R0 group and revised-R1 group. **c.** Comparison of RFS between current-R0 group and current-R1 group. **d.** Comparison of RFS between revised-R0 group and revised-R1 group. RFS tended to be better in the revised-R0 than revised-R1 group (log-rank $p = 0.155$), while this difference was not seen between the current-R0 and current-R1 groups (log-rank $p = 0.576$).

Table 2 Comparison of preoperative and clinicopathological characteristics between current-R0 and current-R1 groups and between revised-R0 and revised-R1 groups.

Variables	current-R0 (n = 84)	current-R1 (n = 16)	p value	revised-R0 (n = 43)	revised-R1 (n = 57)	p value
Age (years)	70 [33–87]	73 [32–82]	0.328	70 [33–87]	70 [32–83]	0.425
Gender			0.878			0.038*
Male	49 (58.3)	9 (56.3)		30 (69.8)	28 (49.1)	
Female	35 (41.7)	7 (43.8)		13 (30.2)	29 (50.9)	
Preoperative treatment	11 (13.0)	2 (12.5)	0.948	8 (18.6)	5 (8.8)	0.148
Tumor location			0.325			0.251
Pancreatic head	53 (63.1)	8 (50.0)		14 (32.6)	29 (50.9)	
Pancreatic body/tail	31 (26.9)	8 (50.0)		29 (67.4)	28 (49.1)	
Portal invasion			0.830			0.814
Positive	24 (28.6)	5 (31.3)		13 (30.2)	16 (28.1)	
Negative	60 (71.4)	11 (68.7)		30 (69.8)	41 (71.9)	
Tumor size (mm)	25 [5–60]	35 [15–80]	0.006*	23 [5–55]	30 [14–80]	<0.001
Lymph node metastasis	42 (50.0)	11 (68.8)	0.168	15 (34.9)	38 (66.7)	0.002*
lymphatic invasion	28 (33.3)	9 (56.3)	0.082	10 (23.3)	27 (47.4)	0.013*
Venous invasion	57 (67.9)	8 (50.0)	0.170	22 (51.2)	43 (75.4)	0.012*
Perineural invasion	67 (79.8)	15 (93.8)	0.182	29 (67.4)	53 (93.0)	0.001*
Adjuvant chemotherapy	52 (61.9)	12 (75.0)	0.317	26 (60.4)	38 (66.7)	0.522
Recurrence pattern						
Liver metastasis	23 (27.4)	7 (43.8)	0.190	10 (23.3)	20 (35.1)	0.201
Local recurrence	25 (29.8)	8 (50.0)	0.115	9 (20.9)	24 (42.1)	0.026*
Peritoneal dissemination	18 (21.4)	4 (25.0)	0.752	6 (14.0)	16 (28.1)	0.092
Lymph node metastasis	6 (7.1)	2 (12.5)	0.469	1 (2.3)	7 (12.3)	0.069

Data are presented as median [range] or n (%). * $p < 0.05$.

There are some limitations in the present study. First, postoperative management, including chemotherapy, was performed by different clinicians. This resulted in an inconsistent quality of patient care. Second, the study was conducted at a single center with relatively few patients. A larger multicenter study is needed to confirm our findings.

In conclusion, the revised classification of R0 resection may be a useful predictor of the prognosis and invasive potential, compared to the current UICC classification for patients with IPDC.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

Statistical analysis was reviewed by Toshiro Katayama Ph.D., the chief statistician in our institution.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.asjsur.2017.09.003>.

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