ORIGINAL ARTICLE

Can the surgeon prolong the remaining life of the patient in pancreaticoduodenectomy surgery? or Is the surgeon helpless?

¿Puede el cirujano prolongar la vida restante del paciente en la cirugía de pancreatoduodenectomía? o ¿El cirujano está indefenso?

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Abstract

Background: *We aimed to evaluate the effects of R0 and R1 resections after pancreatic surgery.* **Methods:** *Data of 130 patients were evaluated. Re-resection was performed in patients who were found to have R1 resection after frozen section (FS). Overall survival (OS), disease free survival (DFS) among patients with R1 resection in paraffin section (PS) (n:28, Group1) and patients who underwent re-resection after FS and achieved the R0 resection goal in PS (n:16, Group 2) (DFS), local recurrence and systemic metastasis results were compared.* **Results:** *Tumor diameter, differentiation, age and complications were found to negatively affect OS. It was observed that DFS increased (p:0.02) and local recurrence rates decreased (p:0.037) in group 2 compared but there was no difference between the two groups in terms of OS (p:0.420) and systemic metastasis (p:0.467).* **Conclusions:** *R0 resection obtained by surgical margin resection of the neck in pancreatic head adenocarcinomas decreases local recurrence and increases the duration of DFS. However, it has no effect on preventing OS and systemic metastasis.*

Keywords: *Pancreas cancer. Surgical margins. Re-resection. Overall survival. Recurrens.*

Resumen

Objetivo. *Nuestro objetivo fue evaluar los efectos de las resecciones R0 y R1 después de la cirugía pancreática.* **Método.** *Se evaluaron los datos de 130 pacientes. La re-resección se realizó en pacientes con resección R1 después de la evaluación congelada (FS). Supervivencia global (SG), supervivencia libre de enfermedad (SSE) (n: 16, Grupo 2) entre los pacientes que se sometieron a resección R1 en sección en parafina (PS) (n: 28, Grupo1) y pacientes que se sometieron a resección después de SF y lograron el Se comparó el objetivo de resección R0 en PS, recidiva local y metástasis sistémica.* **Resultados.** *Se encontró que el diámetro del tumor, la diferenciación, la edad y las complicaciones afectan negativamente la SG. Se observó que la SSE aumentó (p:0,02) y las tasas de recurrencia local disminuyeron (p:0,037) en el grupo 2, pero no hubo diferencias entre los dos grupos en términos de SG (p:0,420) y metástasis sistémica. (p:0,467).* **Conclusión.** *La resección R0 obtenida por resección quirúrgica del margen del cuello en adenocarcinomas de cabeza de páncreas reduce la recidiva local y prolonga la duración de la SSE. Sin embargo, no tiene ningún efecto sobre la prevención de la SG y la metástasis sistémica.*

Palabras clave: *Cáncer de páncreas. Márgenes quirúrgicos. Re-resección. Supervivencia global. Recidiva.*

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Introduction

Despite all efforts and advances in surgery and medical treatment of pancreatic ductal adenocarcinoma (PDAC), it continues to be seen as an aggressive gastrointestinal malignancy with an overall 5-year survival rate of 6 %[1]. There are many factors influencing patient survival following surgery (pancreaticoduodenectomy) for PDCA, such as tumor size, tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), metastasis status of lymph nodes, "T" stage and surgical resection margin[2-4].

But it isn't possible to alter these tumor characteristics and the biological features of the tumor. Despite these negative factors, efforts to increase survival continue. For example, a recent meta-analysis showed that the resection margin is an important prognostic factor for survival of PDAC patients and negative surgical margin is associated with a 12-23 % reduction in mortality risk[5]. Although the effect of resection margin status on patient outcomes is still controversial, the importance of resection margin status in many resectable cancers is that it may have an impact on local recurrence as well as overall survival. This relationship is less clear in pancreatic cancer. Moreover, high local recurrence rates, ranging from 75% to 85%, have been reported following pancreaticoduodenectomy (PD) for PDCA[6].

Until now, frozen section analysis has traditionally taken an important place in the surgical treatment of pancreatic cancer. Although frozen section (FS) analysis is recommended during PD in case of positive surgical margins suspicion, its usefulness is still debated. FS analysis is recommended to extend the resection with repeated sections to obtain the R0 (no tumor cells at the surgical resection margin) surgical margin[7].

When we consider other clinicopathological factors that we know to affect survival in PDCA, obtaining R0 surgical margin with FS analysis seems to be the only modifiable factor that can provide survival benefit. The purpose of this study is to determine the frequency of surgical margin positivity after PD and the necessity or survival benefit of repeated FS analyzes to obtain R0 surgical margin.

Material and methods

This retrospective study was conducted with the Institutional Review Board's approval number 2021-056. All study procedures were performed in accordance with local ethical standards and with the 1964 Helsinki declaration and its amendments.

Study design and study population

All patients who underwent pancreaticoduodenectomy for PDAC from January 2012 to January 2018 were retrospectively evaluated from a prospectively maintained database.

Patients with a diagnosis of benign pathology or with tumors other than PDAC (Neuro-endocrine tumor, distal bile duct tumor, duodenal tumor, ampullary tumor), who received neoadjuvant chemotherapy for borderline PDAC, underwent vena porta resection, and the patients who died at early postoperative period due to non-surgical complications ve SMA surgical margin positivity in PS (n:5) were excluded from the study. Finally, 130 patients who were histopathologically diagnosed with pancreatic ductal adenocarcinoma, met the resectability criteria with multi-detector computed tomography (CT) imaging, and underwent elective pancreaticoduodenectomy were included in the study.

Although the FS result was reported as R0 in 113 patients, it was reported that 27 patients had a tumor at the surgical margin (R1 resection) in PS. These patients formed group 1. In the other 17 patients, it was reported that the tumor continued at the surgical margin of the pancreatic neck in FS. Re-resection was applied to these patients and FS was studied again and R0 resection was achieved. PS results were also reported as R0 in 16 of these 17 patients and these patients formed group 2. In 1 patient, the PS result was reported as R1 resection and was included in group 1 (Fig. 1).

Study variables

The demographic data recorded included the patient's age, gender, re-resection status in patients with positive surgical margins according to FS results, postoperative complication rates after PD, disease free survival (DFS) rates and overall survival (OS) rates. For DFS and OS, 3-year disease-free survival and overall survival after pancreaticoduodenectomy were considered.

Tumor characteristics including histopathological grade, tumor size, surgical margin (uncinate, pancreatic neck, bile duct) status on FS and paraffin section

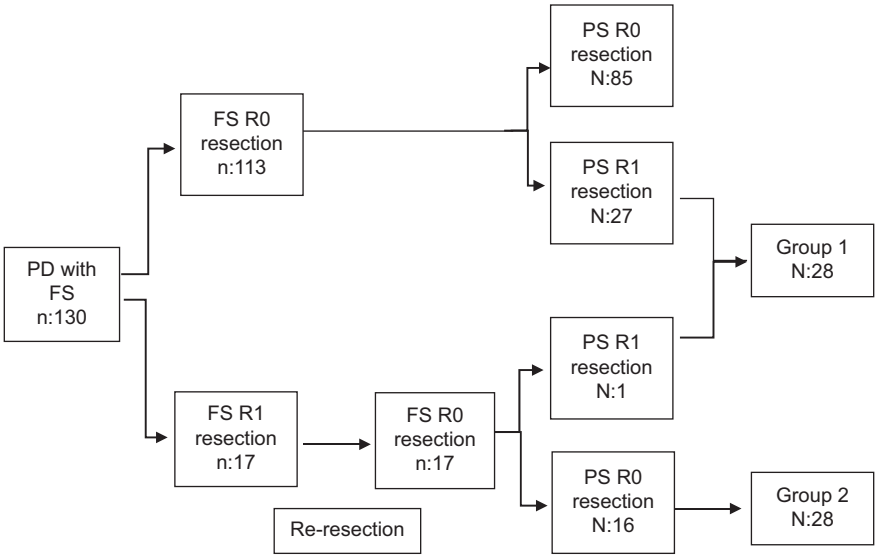

Figure 1. *Flow diagram of study.*

(PS), the lymph node metastasis status, the presence of lymphovascular invasion (LVI) or perineural invasion (PNI) and tumor, node, metastasis (TNM) stage (as per AJCC 7), were recorded after a detailed review of pathology reports.

Surgical technique (Pancreaticoduodenectomy)

All PD procedures were performed by a two gastrointestinal tract surgeons with experience of over 300 pancreaticoduodenectomy surgeries.

All patients who were included in the study underwent standard pancreaticoduodenectomy (without pylor preserving). The transected surgical margins in PD obtained in the following ways: the antrum was divided 3- 4 cm proximal from the pylorus with an Endo GIA™ stapler using a green cartridges. The pancreatic neck was divided with knife in the plane of the SMV-portal vein axis. The bile duct was divided with tissue scissors from where the cystic duct joins the common bile duct. The uncinate process was dissected from retroperitoneum using electrocautery. All pancreaticojejunostomy anastomoses were performed as wirsungojejunostomy anastomosis over the stent.

Evaluation of surgical margins

Surgical margins were routinely evaluated by FS analysis at the pancreatic neck and bile duct after PD. A positive surgical margin was defined as either invasive cancer or high-grade dysplasia. Also if tumor cells were present within 1 mm of the surgical margin in PD analysis, it was considered as “positive surgical margin”.

The terminology used for surgical margins varies widely in publications up to now. For example, Gill and colleagues retrospectively reviewed a number of histopathology reports and found 28 different definitions used to define various PD surgical margins[8]. The terminology of “pancreatic neck margin” is generally universal, but “retroperitoneal”, “uncinate” and “ Superior Mesenteric Artery (SMA) margin” can be synonymous and used interchangeably. In our study, the terminology of the College of American Pathologists (CAP) was used to ensure standardization and as stated in the guidelines of the CAP, “R0 surgical margin” was defined as the macroscopic and microscopic absence of tumor cells, “R1 surgical margin” was defined as the microscopic presence of tumor cells, and “R2 surgical margin” was defined as the presence of a macroscopic tumor[9]. When a positive margin was detected in any surgical margin, the surgical resection was extended until R0 FS result was achieved. All margins were evaluated on PS also.

Since we skeletonized SMA at 180 degrees as the standard technique, we did not perform FS analysis from this area. If a positive FS result was obtained for the Superior Mesenteric Vein (SMV) surgical margin, vein resection and reconstruction was performed. However, these patients were excluded from the study in order not to affect the postoperative morbidity assessment. Similarly, patients with tumor persistence at

the SMA margin in PS were excluded from the study, even if they were detected by FS, because it would not be possible to obtain R0 by re-resection and because their tumor biology was thought to be different.

Outcomes of the study

The primary outcomes were; i) determine the usefulness of surgical margin FS assesment (by the determination of the specificity, sensitivity, positive predictability, negative predictability and accuracy of FS examination), ii) determine the positive surgical margin effect on disease-free survival and overall survival, iii) determine the effect of R0 surgical margin obtained by re-resection on DFS, OS, local recurrence and development of systemic metastasis in PDAC patients treated with PD.

The secondary outcome is to determine the impact of postoperative complications on overall survival.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro–Wilk test. Descriptive analyses were presented using mean±SD (IQR), median (IQR) or n (%), where appropriate. Categorical data were analyzed by Pearson chi-square test. Mann–Whitney U test was used for analysis of non-normally distributed continuous variables. Survival curves were generated by the Kaplan–Meier method, and the log-rank test was used to evaluate differences between groups. Univariate and multivariate analyses of independent predictors of mortality were performed with a Cox proportional hazard regression model. The significant variables in univariate analysis were further tested in the multivariate model. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported. A p-value of less than 0.05 was considered statistically significant.

Standard definitions and calculations such as sensitivity, specificity, accuracy, negative predictive value (NPV) and positive predictive value (PPV) were used for FS diagnostic accuracy measurements.

Results

A total of 130 patients who underwent PD for PDAC between January 2012 to January 2018 were included to the study. Mean age was 67 years (range, 59–74 years), and 44.6 % were females.

Univariate/multivariate and Kaplan-Meier analysis were performed to evaluate the effects of patient and tumor variables on OS. Univariate analysis for factors associated with OS showed that age (p = 0.048), tumor size (p = 0.011), moderatelly/poorly histologic tumor grade (p = 0.024, p = 0.019 respectively) and postoperative complications (p = 0.025) were significantly associated with decreased OS. However, age and tumor size were not an independent prognostic factors of decreased OS on multivariate analysis (p = 0.162, p = 0.585) (Table 1) (Fig. 2).

Frozen was studied from the resection margin of the common bile duct and pancreatic neck in all patients. Although tumor persistence was detected at the surgical margin of the pancreatic neck in 17 patients (13.1%) after FS, no tumor persistence was observed in the common bile duct evaluation. Extended resection was performed in all of these patients until a clean surgical margin (R0 resection) was achieved in FS. However, in 1 of 17 patients, the persistence of the tumor was detected at the surgical margin of the pancreatic neck in PS. In our study, the sensitivity and specificity of FS were determined as 36.3 % and 100 %, respectively, according to the PS result. PPV, NPV were 100% and 75.4%, respectively. Patients with R1 resection after PS (n = 28) formed Group 1, and patients who underwent re-resection after FS and reached the R0 target in PS (n = 16) formed Group 2. Age (p = 0.392), gender (p = 0.187), tumor diameter (0.186), number of lymph nodes removed (p = 0.948), number of positive lymph nodes (p = 0.208), lymphatic invasion (p = 0.208) were compared between the two groups (p = 0.558), PNI (p = 0.376) and stages (p = 0.072) were not significantly different (Table 2).

After re-resections performed on 17 patients with positive surgical margins as a result of FS analysis, it was found that negative surgical margins could not be achieved in one of these patients' PS analyzes. Local recurrence and DFS were positively affected (p = 0.037, p:0.02) but systemic recurrence and OS were not affected by re-resection (p = 0.467, p = 0.420) in patients who achieved the R0 target in PS (Table 3).

Discussion

The aim of this retrospective study is to investigate whether there are any modifiable factors that affect survival in addition to unchangeable tumor characteristics such as size, stage, and differentiation, which are accepted as the main determinants of survival[2,10] in PDAC patients. For example, if we know the area

Table 1. Univariate and multivariate analysis for overall survival

Variables	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
Age	1.016 (1-1.032)	0.048	1.012 (0.995-1.03)	0.162
Male Gender	1.114 (0.755-1.643)	0.587	-	-
Harvested lymph nodes	1.028 (0.991-1.065)	0.136	-	-
Harvested malignant lymph nodes	1.035 (0.965-1.111)	0.335	-	-
Tumor size	1.016 (1.003-1.028)	0.011	1.004 (0.99-1.018)	0.585
T stage				
T0-1	Reference	-	-	-
T2	0.872 (0.471-1.613)	0.662	-	-
T3-4	0.942 (0.505-1.758)	0.851	-	-
N stage				
N0	Reference	-	-	-
N1	1.246 (0.83-1.871)	0.288	-	-
N2-3	1.716 (0.868-3.395)	0.121	-	-
Stage				
Stage 1	Reference	-	-	-
Stage 2	1.068 (0.652-1.749)	0.793	-	-
Stage 3-4	1.244 (0.726-2.134)	0.427	-	-
Lymphatic invasion	1.369 (0.905-2.07)	0.137	-	-
Peri-neural invasion	1.52 (0.945-2.444)	0.084	-	-
Tumor differentiation				
Well differentiated	Reference	-	Reference	-
Moderately differentiated	1.804 (1.081-3.013)	0.024	2.42 (1.39-4.212)	0.002
Poorly differentiated	2.496 (1.162-5.36)	0.019	3.808 (1.684-8.614)	0.001
Complication	1.564 (1.058-2.313)	0.025	1.947 (1.274-2.976)	0.002

Variables with p <0.05 in univariate analysis were included in multivariate model. FS: Frozen section; PS: Paraffin section.

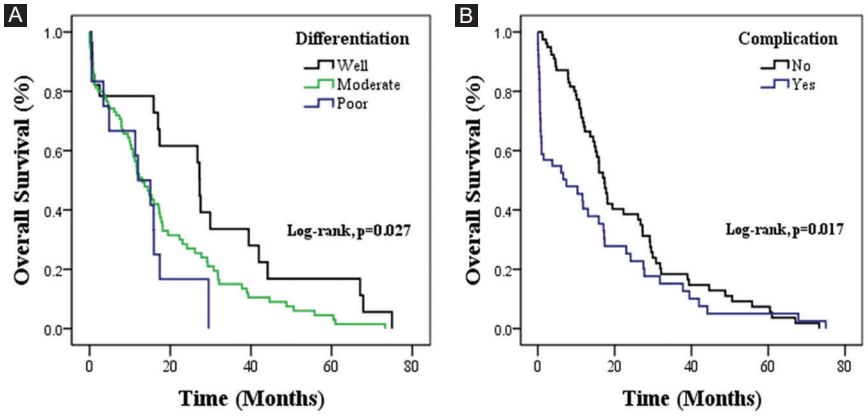

Figure 2. *Kaplan-Meier analysis comparing 5-year overall survival between; A) patients with well, moderate, poor differentiated tumors, B) patients who had postoperative complication or not.*

with the most frequent surgical margin positivity and if we make re-resections in this area to obtain R0 resection margin, can we achieve a survival advantage?

In our study, we determined that unchangeable factors such as age, tumor diameter and differentiation, as well as modifiable factors such as surgical margin

Table 2. Demographic and tumor-related data of patients

	Group 1 n: 28	Group 2 n: 16	Total n: 44	p Value
Age	65,7 ± 10,7	70,0 ± 11,9	67,2 ± 11,2	0,392
Tumor size (mm)	33,1 ± 15,3	40,8 ± 19,3	35,9 ± 17,1	0,186
Harvested LN	11,7 ± 6,9	15,1 ± 6,6	12,9 ± 12,9	0,948
Tumor Positive LN	1,6 ± 2,4	2,3 ± 3,5	1,8 ± 2,8	0.208
Gender				
Female	14 (50%)	5 (31,3%)	19 (43,2%)	0,187
Male	14 (50%)	11 (68,8%)	25 (56,8%)	
Lymphatic invasion	21 (77,8%)	12 (75,0%)	33 (76,7%)	0,558
PNİ	25 (89,3%)	13 (81,3%)	38 (86,4%)	0,376
Morbidity	9 (32,1%)	7 (43,8%)	16 (36,4%)	0,326
T Stage				
T2	18 (64,3%)	7 (43,8%)	25 (56,8%)	0,416
T3	9 (32,1%)	8 (50%)	17 (38,6%)	
T4	1 (3,6%)	1 (6,3%)	2 (4,5%)	
N Stage				
N0	9 (32,1%)	5 (31,3%)	14 (31,8%)	0,232
N1	17 (60,7%)	7 (43,8%)	24 (54,5%)	
N2	2 (7,1%)	4 (25,0%)	6 (13,6%)	
Tumor stage				
I	6 (21,4%)	1 (6,2%)	7 (15,5%)	0,072
II	10 (35,7%)	10 (62,5%)	20 (45,5%)	
III	12 (42,9%)	5 (31,3%)	17 (38,6%)	
Komplikasyon	11 (39.2%)	6 (37.5%)	17 (38.6%)	0,726
Diferansiasyon				
Well	6 (21.4%)	3 (18.8%)	9 (20.5%)	0.812
Moderate	19 (67.8%)	11 (68.8%)	30 (68.2%)	
Poor	3 (10.8%)	2 (12.4%)	5 (11.3%)	

positivity and postoperative complications affect overall survival. However, we found that re-resections performed upon detection of a positive surgical margin in FS did not provide an OS and systemic metastasis benefit. But it can positively affect to DFS and loco regional recurrence. On the other hand the occurrence of postoperative complications negatively affected OS.

R0 tumor resection has been shown one of the main determinant of the outcomes of the patients with pancreas neoplasm[11] and therefore, positive surgical margins determined in frozen section analysis are commonly re-resected by extending resection margins to obtain margin negative resection. However, studies evaluating the effect of surgical margin status on overall survival in PDAC are conflicting. While some studies indicate a significant survival difference between patients with negative and positive surgical margins, some others have shown no difference in OS[12-14].

In addition, the methodologies of the studies differ significantly. This prevents to comment on the contribution of FS analysis to OS and DFS. The most important problems in these study cohorts are; i) evaluating benign and malignant pancreatic tumors together, ii) not clearly specifying surgical margins, iii) heterogeneity in surgical margin definitions, iv) significant differences about sensitivity and specificity data of FS analysis. There are also very few data in the literature about the contribution on survival of surgical margins positivity and re-resections. In our study, we tried to minimize the variables that could affect the results by excluding patients without pancreatic adenocarcinoma, defining the surgical margins clearly, and ensuring that all PD

Table 3. DFS evaluation of the patients with positive surgical margins in PS analyzes and the patients with negative surgical margin after re-resection

	Patients with positive surgical margin in PS n: 28 (Group 1)	Patients with negative surgical margin in PS after re-resection n: 16 (Group 2)	Total	p
Loco regional recurrence	12 (42.9%)	2 (12.5%)	14 (31.8%)	0.037
Systemic metastasis	14 (50%)	7 (43.8%)	21 (47.7%)	0.467
DFS (mean) (day)	200.4 ± 175.6	356.3 ± 249.4	257.1 ± 216.4	0.02
OS (mean) (day)	398.6 ± 418.5	512.1 ± 488.5	439.9 ± 443.1	0.420

DFS: Disease free survival; PS: Paraffin section
[a]Pearson Chi-Square, [b]Oneway ANOVA

applications were performed by two experienced gastrointestinal surgeons.

In some studies, it has been reported that the surgical margin of the SMA (Retroperitoneal) is the area that is frequently found to be positive, and this positivity is associated with a poor prognosis due to independent factors[15]. We did not routinely evaluate the surgical margin of SMA with FS, since we performed the resection of this region to the maximum extent in each patient and there was no definitive evidence of the benefit of arterial resection in case of FS positivity in this region. Again, we did not include patients in the R1 resection group[16] due to the worse prognosis of patients (n:5) with this region positivity in PS.

There have been authors who stated that total pancreatectomy increased overall survival[17] and in addition to determining the surgical margin for PDAC, FS analysis must be as the standard care in distinguishing cystic neoplasms and intraductal papillary mucinous neoplasms[18-20]. However, in our study, we observed that the negative surgical margin obtained with re-resections did not provide any survival benefit.

Although surgical margin positivity was defined by some authors as an indicator of aggressive tumor biology and diffuse micrometastatic disease, in our study, although margin positivity negatively affected DFS and locoregional recurrence, no significant effect was observed in terms of systemic metastasis and OS[3-12].

Another dilemma in the literature is the true accuracy of this test, both in margin positivity and in assessing margin histopathology, has never been accurately evaluated. However, when the literature is evaluated, according to some authors, the accuracy of the FS analysis was poor and there were unacceptably high false-negative results of up to 12%[21]. On the other hand, Zheng et al. stated in their recently evaluated cohorts with 1076 patients that intraoperative FS evaluation was highly sensitive and has 90.6 % negative predictive value[22]. In our study, we found the sensitivity and specificity of FS as 36.3 % and 100 %, respectively.

We also observed that postoperative complications negatively affect overall survival in our study. The most common complication we observed was pancreatic fistula with a rate of 26.2%. Pancreatic fistula classification was made according to the classification published by the "International Study Group of Pancreatic Fistula" working group in 2016[23]. The effect of PF on overall and disease free survival in pancreatic cancer is controversial in english literature. Although there are a few studies on this subject, different results have been obtained. For example, Murakami and Assifi reported that PF had no effect on OS and DFS in their series, while Nagai concluded that PF may be a negative prognostic factor in pancreatic cancer patients[4,24]. Neeman et al. in their recent study, found no relationship between postoperative PF and overall survival or disease-free survival in patients who underwent PD for PDAC[25]. In our study, both multivariate and univariate analysis, we observed that overall survival was negatively affected in patients with postoperative complications. Although there is no definite information in the literature about the mechanism of the negative effect of complications on OS, we think that this may be related to the delay in the oncological treatment of the patient and the negative impact of the patient's immune system.

There are some limitations in our study. The first of these is that it was done retrospectively and with a small number of patients. Others are that we could not compare patients with positive pancreatic neck

surgical margins due to the low number of patients with positive SMA surgical margins. In addition, since the patients in our study consisted of pancreatic head adenocarcinomas, it does not give an idea about the surgical margin evaluations in other periampullary region tumors.

In our study, we found that re-resections performed to reach the R0 target at the pancreatic neck surgical margin in PD surgeries for pancreatic head cancer reduced local recurrence and increased DFS, but had no effect on the increase in OS and the reduction of systemic metastasis.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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