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Intra-Operative Frozen Section Histology of the Pancreatic Resection Margins and Clinical Outcome of Patients with Adenocarcinoma of the Head of the Pancreas Undergoing Pancreaticoduodenectomy

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Background: The aim of this study was to compare the clinical outcome in patients with pancreatic ductal adenocarcinoma who underwent frozen section and paraffin section histology of the surgical resection margins during pancreaticoduodenectomy.

Material/Methods: Frozen section and routine paraffin section histopathology were performed using the following categories: R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin). R1 and R2 patients underwent additional resection to achieve R0.

Results: Of 346 patients who underwent pancreaticoduodenectomy, frozen section histology showed positive resection margins in 22 patients (9.2%) and paraffin section histology was positive in 20 patients (8.4%). The OS was nine months in frozen section-positive patients and 20 months in frozen section-negative patients (p=0.001). The OS rates were significantly different between the paraffin section-positive and paraffin section-negative patients (11 months *vs.* 21 months) (p=0.001). Univariate and multivariate analysis showed that increased tumor size, high tumor grade, lymph node metastases, a positive superior mesenteric artery and retroperitoneal margin, and a positive resection margin on frozen section were significantly correlated with reduced OS (p<0.05). Twenty-two patients with positive resection margins on frozen section histology underwent further resection; R0 was achieved in 14 patients, with no significant difference in OS.

Conclusions: For patients who underwent pancreaticoduodenectomy for pancreatic carcinoma with positive resection margins on frozen section, further surgical resection to achieve R0 had no significant positive impact on OS.

MeSH Keywords: Carcinoma, Pancreatic Ductal • Frozen Sections • Pancreaticoduodenectomy • Survival

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Background

Worldwide, pancreatic cancer represents approximately 10% of all gastrointestinal cancers and ranks fourth for cancer-related mortality [1,2]. Ductal adenocarcinoma of the pancreas has high mortality when compared with other gastrointestinal cancers, is difficult to diagnose early, and the primary treatment is surgical excision, or pancreaticoduodenectomy (Whipple procedure) [3,4]. However, only 20% of cases of ductal adenocarcinoma are surgically resectable at diagnosis [3,4]. The overall 5-year survival rate for patients with adenocarcinoma of the pancreas is less than 5% at diagnosis [5,6].

Despite recent developments in surgical and medical treatment, pancreatic cancer still has a poor prognosis. Tumor size, tumor stage, tumor grade, lymph node status, the presence of lymphovascular and perineural invasion, and a positive surgical resection margin are the main prognostic factors, which have been confirmed by previous clinical studies [7–14]. Of the prognostic factors for patients with pancreatic carcinoma, the surgeon can influence or modify the status of the surgical resection margin, the extent of lymph node dissection, and patient selection, all of which can affect the overall survival (OS) rate of the patient, but other prognostic factors cannot be modified surgically [6–14]. According to the recommendations of the International Union Against Cancer (UICC) (*www.uicc.org*) and the American Joint Committee on Cancer (AJCC) (*www.cancerstaging.org*), evaluation of the surgical resection margins are categorized as R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin).

Several previously published studies have shown that patient prognosis in pancreatic adenocarcinomas is affected by an R0 resection margin at pancreaticoduodenectomy, and R0 has been shown to be an independent prognostic factor for long-term survival rates [10,15,16]. However, some studies have reported that no significant difference could be demonstrated between R0 and R1 resections on long-term survival rates [10,11,17,18]. These conflicting results could be explained by the surgical techniques, the experience of the pathologist evaluating the specimens, and the biology of the tumor.

During pancreaticoduodenectomy, the pancreatic neck resection margin, superior mesenteric artery and retroperitoneal resection margin, the bile duct resection margin, and the intestinal resection margin are also evaluated. In the case of positive superior mesenteric artery and retroperitoneal surgical resection margins, additional surgical resection cannot be performed. However, if a positive pancreatic neck surgical margin is detected by intraoperative analysis of the frozen section histology, an additional resection can be performed. Previously published studies have shown that an R0 margin, diagnosed by intra-operative frozen section histology, has a positive impact on patient survival rate [10,18,19]. However, other studies have shown that intraoperative frozen section analysis had no impact on long-term survival rates, but it can increase the rate of diagnosis of R0 [9,11,17,20].

Therefore, the aim of this study was to compare the clinical outcome in terms of OS in patients with pancreatic ductal adenocarcinoma who underwent frozen section and paraffin section histology of the surgical resection margins during pancreaticoduodenectomy.

Material and Methods

Ethical approval

All procedures involving human study participants were performed in accordance with local ethical standards and with the approval of the Local Institutional and National Research Committees and with the 1964 Helsinki declaration and its amendments. All patients provided written informed consent to undergo the surgical and diagnostic procedures used in this study.

Patients studied and study design

A prospective observational study analyzed data from 346 patients who underwent pancreaticoduodenectomy (Whipple procedure) in the Medical Faculty Hospital of Gazi University, Ankara, Turkey between October 2008 and June 2016. A total of 238 patients with a histopathological diagnosis of pancreatic ductal adenocarcinoma were enrolled in the study. All patients were examined using multidetector computed tomography (CT) imaging, and patients who fulfilled the criteria for tumor resectability underwent elective pancreaticoduodenectomy and were included in the study. There were 108 patients who were excluded from the study due to a histopathological diagnosis of distal bile duct tumor, ampullary tumor, neuroendocrine tumor, duodenal tumor, intraductal papillary mucinous neoplasm, solid pseudopapillary tumor, or chronic pancreatitis. Patients were also excluded from the study if they had distant metastasis, the involvement of the superior mesenteric artery of more than 180 degrees, hepatic artery invasion, and macroscopic residual tumor at the resection margins following tumor resection (R2).

Clinical study variables

Demographic data recorded included patient age, sex, the use of neoadjuvant chemotherapy or radiotherapy, and the use of resection of the portal vein or the superior mesenteric vein.

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The characteristics of the tumor were also recorded, including the tumor size (cm), the histopathological grade, the tumor, node, metastasis (TNM) stage, according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition), lymphovascular invasion, perineural invasion, pancreatic neck margin status on frozen section and on paraffin section histology, final surgical margin histology of the resection specimen, the lymph node metastasis status, the follow-up period, and overall survival (OS) rates.

Pancreaticoduodenectomy

All patients who were included in the study underwent standard pancreaticoduodenectomy, with resection of the pancreas performed with cauterization. During surgery, frozen section analysis was routinely performed for the pancreatic tissue at the resection margin of the pancreatic neck. Additional resection was performed in patients who had a positive frozen section diagnosis (R1), to achieve a negative surgical margin (R0). Postoperative routine formalin-fixed, paraffin-embedded (FFPE) tissue sections (paraffin sections) were examined histologically using routine diagnostic laboratory methods.

Categories of surgical resection margin status (R0, R1, and R2)

Surgical margin status was evaluated with frozen section and paraffin section histology according to the recommendations of the International Union Against Cancer (UICC) (*www.uicc.org)* and the American Joint Committee on Cancer (AJCC) (*www.cancerstaging.org*). The surgical resection margins were categorized as: R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin). Patients with R2 resection status were excluded from the study because the number of patients who had R2 resection margins was small.

Categories of patients included in the study according to resection margin status on frozen section and paraffin section histology

The focus of this study was to evaluate the role of intraoperative frozen section histology to detect R0 and R1 surgical margins and to follow up these findings with the later examination of the formalin-fixed, paraffin-embedded or paraffin sections which were available for histopathology several hours postoperatively. Patients were divided into groups according to their surgical resection margin properties. Patients with negative frozen section and paraffin section histology (R0 on frozen section and R0 on paraffin section); patients with negative frozen section histology and positive paraffin section histology (R0 on frozen section and R1 on paraffin section); patients

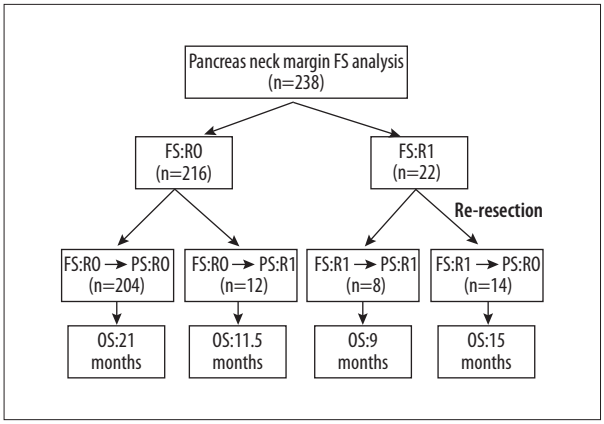

Figure 1. The distribution of patients who underwent a pancreatic neck margin frozen section and routine formalin-fixed, paraffin wax-embedded section histopathology.

with positive frozen section histology and negative paraffin section histology (R1 on frozen section and R0 on paraffin section); and patients who had additional resection because of positive frozen section histology, but who remained R1 in paraffin section histology (R1 on frozen section and R1 on paraffin section). Survival rates were calculated from the day of surgery. The distribution of patients by pancreatic neck margin frozen section and paraffin section status is shown in Figure 1.

Statistical analysis

The software package SPSS version 21.0 was used for statistical analysis. Complementary statistics were presented as the frequency, percentage distribution, the mean, and the median. The chi-squared (χ^2) test was used for the comparison of qualitative variables. The Kruskal-Wallis test was used for the four-group comparison of quantitative variables, and the Mann-Whitney U test was used for the comparison of two groups. The Kaplan-Meier log-rank test was used to show the impact of the variables on overall survival (OS0. Variables that were significant at $p<0.05$ in univariate analysis were analyzed with the multivariate Cox regression method, and 95% confidence intervals (CI) were calculated with hazard ratio (HR) values. The accepted level of significance was $p<0.05$.

Results

Patients and clinical characteristics

This study investigated the surgical margins of 238 patients who underwent pancreaticoduodenectomy (Whipple procedure) for pancreatic ductal adenocarcinoma. All surgical procedures were performed in Gazi University Faculty of Medicine between October 2008 and June 2016. The authors of this

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Table 1. Demographic, operative, and pathological characteristics of all patients.

Variable	All patients (n=238)	FS: R0–PS: R0 (n=204)	FS: R0–PS: R1 (n=12)	FS: R1–PS: R0 (n=14)	FS: R1–PS: R1 (n=8)	P value
Mean age (years)	64 (29–90)	65 (29–90)	64 (49–79)	63 (42–77)	62 (54–77)	0.971
Sex (male)	148 (62.2%)	124 (60.8%)	10 (83.3%)	8 (57.1%)	6 (57.1%)	0.367
Tumor size (cm)	3.1±1.2	3.1±1.3	3.5±1.3	3.1±1.1	3.5±1.0	0.572
PV/SMV resection	16 (6.7%)	10 (4.9%)	–	6 (42.9%)	–	**0.001**
Neoadjuvant CT	4 (1.7%)	4 (2%)	–	–	–	0.878
OS (months)	19 (1–85)	21 (7–85)	11.5 (9–16)	15 (3–33)	9 (1–25)	**0.001**
Histologic grade						
Well differentiated	82 (34.5%)	70 (34.3%)	4 (33.3%)	6 (42.9%)	2 (25%)	0.709
Moderately differentiated	118 (49.6%)	100 (49.0%)	8 (66.7%)	6 (42.9%)	4 (50%)	
Poorly differentiated	38 (16%)	34 (16.7%)	–	2 (14.3%)	2 (25%)	
SMA/RP margin positivity	92 (38.7%)	62 (30.4%)	12 (100%)	10 (71.4%)	8 (100%)	**0.001**
T stage						
T1	4 (1.7%)	4 (2%)	–	–	–	0.574
T2	14 (5.9%)	14 (6.9%)	–	–	–	
T3	210 (88.2%)	178 (86.3%)	12 (100%)	12 (85.7%)	8 (100%)	
T4	10 (4.2%)	8 (3.9%)	–	2 (14.3%)	–	
LN positivity	176 (73.9%)	146 (71.5%)	12 (100%)	14 (100%)	4 (50%)	**0.041**
LVI positivity	208 (87.3%)	178 (87.2%)	12 (100%)	10 (71.4%)	8 (100%)	0.321
PNI positivity	224 (94.1%)	192 (94.1%)	10 (83.3%)	14 (100%)	8 (100%)	0.273

study performed the surgery on these patients. Demographic characteristics, intraoperative characteristics, and pathological properties of the tumors are shown in Table 1. The mean age of the 238 patients was 64 years (range, 29–90 years), and 62.2% were men (148/238). Among these patients, 6.7% (n=16) underwent portal vein or superior mesenteric vein resection. Neoadjuvant chemotherapy was administered to only 1.7% of the patients. The calculated median overall survival (OS) was 19.0 months, and the mean tumor size was 3.0 cm (range, 0.3–11 cm).

Pancreatic ductal adenocarcinoma histopathology and stage

Histopathological examination of the tumors showed the following tumor grades: well-differentiated in 82 patients (34.5%); moderately-differentiated in 118 patients (49.6%); and poorly-differentiated in 38 patients (16%). Also, 73.9% of the patients had at least one metastatic lymph node, while 87.3% of the patients had histological pancreatic lymphovascular invasion, and 94.1% had perineural invasion. In 88.2% of patients (n=210), the tumor stage was T3, and in 38.7% of patients (n=92) the superior mesenteric artery and the retroperitoneal surgical margin were positive.

Patient overall survival (OS)

The findings of the univariate analysis performed for OS-related factors are shown in Table 2. Reduced patient OS was correlated with an increase in tumor size (p=0.001), poorly-differentiated histological grade (p=0.001), the presence of a metastatic lymph node (p=0.001), and positive superior mesenteric artery and retroperitoneal resection margin (p=0.001). Multivariate Cox regression analysis (Table 2) showed that reduced patient OS was correlated with increased tumor size (HR=1.3; 95% CI, 1.1–1.5; p=0.001), moderately-differentiated or poorly-differentiated tumor (HR=2.0; 95% CI, 1.7–2.9; p=0.001, and HR=2.5; 95% CI, 1.5–3.1; p=0.001, respectively), positive superior mesenteric artery and retroperitoneal resection margins (HR=1.6; 95% CI, 1.1–2.3; p=0.03), the presence of metastatic

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Table 2. Univariate and multivariate analysis of clinicopathologic factors associated with overall survival, including final pancreatic neck margin status.

Variable	Univariate			Multivariate		
	HR	98% CI	P Value	HR	98% CI	P Value
Tumor size (cm)	1.3	1.1–1.4	0.001	1.3	1.1–1.5	0.001
Histopathologic grade						
Well differentiated	Ref			Ref		
Moderately differentiated	1.1	0.7–1.6	0.47	2.0	1.7–2.9	**0.001**
Poorly differentiated	2.2	1.3–3.5	**0.001**	2.5	1.5–3.1	**0.001**
LVI	1.0	0.8–1.3	0.43	2.0	0.8–2.8	0.68
PNI	1.0	0.8–1.6	0.60	1.2	0.3–4.2	0.67
MLN	1.2	1.1–1.3	**0.001**	1.2	1.1–1.8	**0.001**
SMA/RP margin	2.4	1.7–3.4	**0.001**	1.6	1.1–2.3	**0.03**
SMV/PV resection	1.4	0.6–1.7	0.49	1.0	0.4–2.5	0.59
FS positivity	2.3	1.4–3.8	**0.001**	2.2	1.2–3.8	**0.008**
PS positivity	4.4	2.6–7.4	**0.001**	4.1	2.2–7.8	**0.001**
Neck margin status						
FS: R0→PS: R0	Ref			Ref		
FS: R0→PS: R1	4.5	2.1–9.4	**0.001**	3.5	2.5–8.9	**0.008**
FS: R1→PS: R0	4.8	2.5–9.1	**0.001**	3.7	2.7–9.1	**0.008**
FS: R1→PS: R1	1.1	0.5–2.6	0.69	1.7	0.8–1.9	**0.47**

CI – indicates confidence interval; HR – hazard ratio. Bold values are statistically significant.

lymph nodes (HR=1.2; 95% CI, 1.1–1.8; p=0.001), the presence of positive margins in frozen section analysis (HR=2.2; 95% CI, 2.2–3.8; p=0.008), and positive final paraffin section pancreatic neck margin analysis (HR=4.1; 95% CI, 2.2–7.8; p=0.001). On multivariate analysis, vascular resection and the presence of lymphovascular invasion and perineural invasion were not correlated with decreased OS.

Categories of involvement of the resections margin

Evaluation of the resection margin of the neck of the pancreas included the categories: R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin), with R2 cases excluded from the study. The main objective of our study was to investigate the impact of additional resections carried out to achieve R0 in paraffin section analysis for patients with positive pancreatic neck surgical margins diagnosed on intra-operative frozen section histology. Additional resection was performed in patients with positive frozen section analysis, which was done to determine the pancreatic neck margin. In 14 of these patients, R0 was diagnosed on paraffin section histology (R1 on frozen section and R0 on paraffin section), but it could not be achieved in 8 patients (R1 on frozen section and R1 on paraffin section). In 204 patients a negative resection margin on frozen section histology was confirmed on paraffin section histology (R0 on frozen section and R0 on paraffin section). The pancreatic neck margin was evaluated as R1 in the final paraffin section analysis in only 12 patients, although frozen section analysis indicated R0 (R0 on frozen section and R1 on paraffin section). Histological findings of the tumor resection margins are shown in Table 1.

Involvement of the resection margins and patient overall survival (OS)

Frozen section analysis was performed for all patients. The results of intra-operative frozen section histology showed that 22 patients (9.2%) had positive pancreatic neck margins. Postoperative paraffin section histology showed that 20 patients (8.4%) had positive pancreatic margins (R1). Regardless of the final paraffin section margin histology, there were significantly lower OS rates of patients who had positive pancreatic

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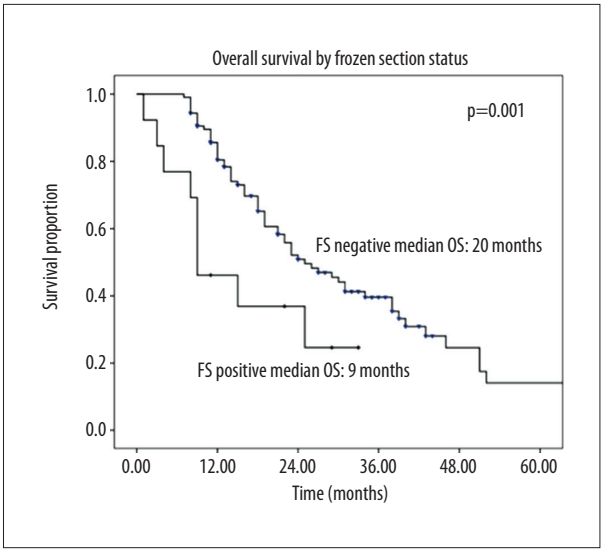

Figure 2. Overall survival (OS) of patients who had a pancreatic neck margin frozen section.

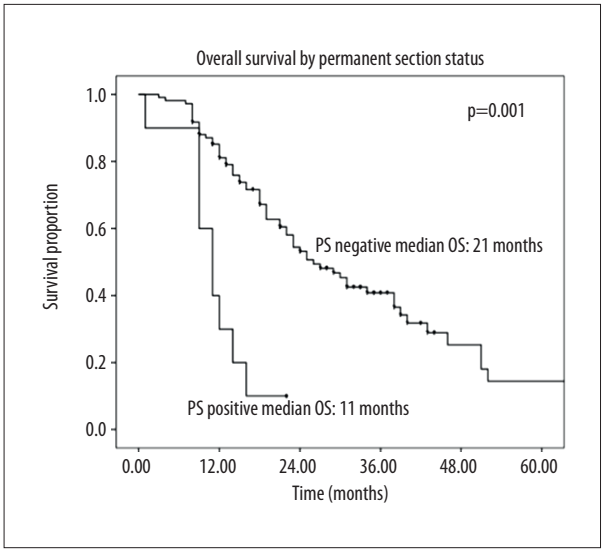

Figure 3. Overall survival (OS) of patients who had routine formalin-fixed, paraffin wax-embedded section histopathology.

neck margins in the intraoperative frozen section histology compared with patients who had negative frozen section analysis (9 months *vs.* 20 months) (p=0.001) (Figure 2). Also, the mean OS was 11 months in patients with R1 in the paraffin section histology of the pancreatic neck resection margin, and 21 months in patients with R0 in the paraffin section histology (p=0.001) (Figure 3). The difference between the mean OS rates was not statistically significant (15 months *vs.* 9 months) (p=0.17) between 14 patients who were R1 on frozen section histology, but became R0 in later paraffin section histology (R1 on frozen section and R0 on paraffin section), and eight patients who did not become R0 on paraffin section histology (R1 on frozen section and R1on paraffin section).

Discussion

Currently, the most effective treatment option for pancreatic ductal adenocarcinoma of the head of the pancreas is pancreaticoduodenectomy (Whipple procedure). The risk factors that are associated with low patient survival rates in completely resected tumors include increased tumor size, the presence of lymphovascular invasion and perineural invasion, lymph node metastasis, poor (high) histological grade, and a positive surgical resection margin. Among these risk factors, a clear surgical resection margin and adequate lymph node dissection are directly affected by the surgical technique and by the experience of the surgeon.

The histological evaluation of the surgical resection margins is important in preventing tumor recurrence. In the present study, the surgical resection margin status was evaluated with frozen section and paraffin section histology according to the recommendations of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) as: R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin). Patients with R2 resection status were excluded from the study because the number of patients who had R2 resection margins was small. In patients with positive frozen section results obtained with a specimen from the pancreatic neck, additional resection was performed to achieve R0. The surgical resection margins of the superior mesenteric artery, retroperitoneal margin, bile duct, and pancreatic margin status are variables that can be evaluated separately. However, among these surgical margins, the pancreatic neck resection margin was evaluated and correlated with overall survival (OS).

In cases of a positive pancreatic neck margin in intraoperative frozen section analysis, the final margin status in paraffin section analysis might become R0 with additional resection or resections. However, this status raises the question of the possible benefits with respect to long-term survival rates. Several previously published studies conducted at specialized surgical centers at with a high volume of pancreatic surgical procedures have shown that R0 diagnosed by intra-operative frozen section, followed by additional surgical resection might have a positive impact on survival rates [10,15,16]. However, other studies have shown conflicting findings [10,11,17,18]. Therefore, the objective of this study was to evaluate the impact of the confirmation of the finding on frozen section histology with that of paraffin section histology on long-term survival rates in patients who underwent pancreaticoduodenectomy,

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including for patients with both R0 and R1 intra-operative frozen section histology.

In the present study, the mean OS rates for the patients who had negative pancreatic neck surgical margins on frozen section histology were significantly greater compared with patients with frozen section-positive histology, regardless of the results of paraffin section analysis (20 months *vs.* 9 months) (p=0.001). These findings are supported by those of, Lad et al., who reported that a positive pancreatic neck surgical excision margin on frozen section histology (R1) was associated with poor patients survival, but that extending the neck resection to achieve an R0 margin did not improve OS (mean OS of 17.3 months in R0 patients and 11.1 R1 patients) [21]. In 2013, a study by Kimbrough et al. showed that patients with R0 resection margins, compared with R1 resection margins, had both improved OS (22.7 months *vs.* 15.0 months) (P=0.004) and disease-free survival (13.5 months *vs.* 10.7 months) (P=0.026) [20]. However, in the present study, frozen section-positive pancreatic neck surgical margin was an independent factor for OS in multivariate Cox regression analysis. However, OS was significantly increased in the patients who underwent additional resection due to frozen section-positive margins who had R0 on paraffin section histology (R1 on frozen section and R0 on paraffin section), compared with patients who were R0 on intraoperative frozen section and who were R0 on postoperative paraffin section (R0 on frozen section and R0 on paraffin section). However, the mean survival rates of the following groups were similar with no statistical difference between the groups: R0 on frozen section and R1 on paraffin section; and R1 on frozen section and R1 on paraffin section.

The findings of the present study are not only supported by those of Lad et al. [21], but also by Kooby et al. [13], who showed that the survival rates were comparable between patients who had R0 resection margin status after additional resection, and patients who were R1 in the paraffin section analysis. However, in these studies, the resection margins were evaluated in the R0 and R1 groups by both frozen section and paraffin section histology, but the final paraffin section analysis included the R1 group [13,21]. However, in the present study, an additional resection was performed for all frozen section-positive patients. Regardless of the additional resection, positive lymph nodes, increased tumor size, histological grade, and the presence of lymphovascular invasion and perineural invasion were found to be associated with paraffin section-positive (R1) compared with paraffin section-negative (R0) patients (Table 1). Similar to previously published studies, the findings of the present study confirmed that aggressive tumor biology is correlated directly with tumor involvement of the pancreatic neck surgical margin [18,22].

Although the findings of previously published studies to compare the clinical outcome in patients with pancreatic ductal adenocarcinoma who underwent frozen section and paraffin section histology of the surgical resection margins during pancreaticoduodenectomy have shown some conflicting findings overall, the findings in the literature tend to support the findings of the present study [9,11,23]. Dillhoff et al. reported that additional surgical resection did not correlate with a significantly improved mean OS rate (21.7 months *vs.* 14.6 months) (p=0.20) [9]. Dillhoff et al. suggested that the most important factor correlating with patient OS was the presence of positive lymph nodes, and therefore, tumor biology was more important than the presence of tumor at the surgical resection margin [9]. Hernandez et al. reported similar results to those reported in the present study, with the mean OS reported as 21 months in R0 patients, 13 months in R1 patients, and 11 months in R1 to R0 patients [11]. Also, Hernandez et al. showed that there was a more important relation between positive lymph nodes (an indicator of tumor biology) than the status of the surgical resection margin [11]. However, in this previously published study [11], the study design differed, as the superior mesenteric artery, retroperitoneal, and bile duct surgical margins were analyzed in addition to the pancreatic neck surgical margin. Neoptolemos et al. [24] reported that the OS rates of patients with R0 resection margins were significantly greater compared with the OS rates of patients with R1 resection margins (R0, 16.9 months *vs.* R1, 10.9 months) ($p \leq 0.05$). However, previously published meta-analysis data has also reported that the resection margin does not have an impact on OS and that the prevalence of R1 resection margin status has a broad range from 25–80% [7,24–27]. It is also possible that the range of differences in the prevalence of the R1 status in the surgical resection margins during pancreaticoduodenectomy might depend on the differences of the methods of evaluation of the resected specimen, both intra-operatively and postoperatively.

Although the majority of previously published studies support the findings of the present study, there have been some conflicting results, which have suggested more aggressive surgical interventions should be performed to achieve an R0 margin [18,28,29]. Fatima et al. reported that the OS rates of patients who were R1 frozen section-positive but became R0 after additional resections were similar to those of patients who were R0 intra-operatively and that these rates were significantly higher than those of patients who were R1 in paraffin section analysis [10]. Also, Schmidt et al. carried out total pancreatectomy in patients to achieve an R0 margin and showed that OS rates increased significantly in patients who achieved R0 [18]. Because there remains no clear consensus regarding further resection for patients with pancreatic ductal adenocarcinoma undergoing pancreaticoduodenectomy who have positive intra-operative resection margins on frozen

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section histology, and that surgical margin status might be affected by more aggressive tumor biology, the risk/benefit ratio of total pancreatectomy, which has high morbidity and mortality rates, should be evaluated cautiously.

This study had several limitations, including small subject study size obtained from a single center and the lack of a standardized method of sampling and histopathological evaluation of the surgical resection margin. The main limitation of this study was that the duration of the study and length of patient follow-up did not allow for long-term evaluation of the tumor recurrence rates at the pancreatic neck margin. The results of the study should not be interpreted as supporting the lack of further surgical intervention when patients with pancreatic ductal adenocarcinoma have positive surgical resection margins during pancreaticoduodenectomy. It is important to continue to study and improve the techniques for intra-operative evaluation of the completeness of surgical excision for patients with pancreatic ductal adenocarcinoma and to continue to evaluate other prognostic factors in patients with this type of cancer, together with improvements in non-surgical treatment approaches.

Conclusions

The aim of this study was to compare the clinical outcome in patients with pancreatic ductal adenocarcinoma who underwent frozen section and paraffin section histology of the surgical resection margins during pancreaticoduodenectomy. The findings of this study supported that for patients with frozen section-positive resection margins (R1), additional resection might achieve a tumor-free margin (R0), but the findings from this study showed that this had no significant impact on overall survival (OS). Although the findings of this study do not resolve the continuing controversy regarding the necessity of intra-operative frozen section diagnosis during surgery, the findings do contribute to the literature in this aspect of the management of patients with pancreatic ductal adenocarcinoma.

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Conflict of interest

None.

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