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ORIGINAL ARTICLE – PANCREATIC TUMORS

Is it Time to Stop Checking Frozen Section Neck Margins During Pancreaticoduodenectomy?

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ABSTRACT

Background. Residual disease after pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma (PDAC) adversely impacts survival. The value of taking additional neck margin after a positive frozen section (FS) to achieve a negative margin remains uncertain.

Methods. All patients who underwent PD for PDAC from January 2000 August 2012 were identified and classified as negative (R0) or positive (R1) based on final neck margin. We examined factors for association with a positive FS neck margin and overall survival (OS). We assessed the value of converting an R1 neck margin to R0 via additional parenchymal resection.

Results. A total of 382 patients had FS neck margin analysis, of which 53 (14 %) were positive. Positive FS neck margin was associated with decreased OS (11.1 vs. 17.3 months, $p = 0.01$) on univariate analysis. On multivariate analysis poor histologic grade ($p = 0.007$), increased tumor size ($p = 0.003$), and a positive retroperitoneal margin ($p = 0.009$) were independently associated with decreased OS, but positive FS neck margin was not. Of the 53 patients with positive FS, 41 underwent additional neck resection and 23 were converted to R0. On permanent section, R0 neck margin was achieved in 322 patients (84 %), R1 in 37 patients (10 %), and R1 converted to R0 in 23 patients (6 %). Both the converted and the R1 groups had significantly poorer OS than the R0 group (11.3 vs. 11.1 vs. 17.3 months respectively; $p = 0.04$).

Conclusions. Positive FS margin at the pancreatic neck during PD for PDAC is associated with poor survival. Extending the neck resection after a positive FS to achieve R0 margin status does not appear to improve OS.

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality in the U.S.[1] It is a highly aggressive malignancy and surgery remains the only potentially curative treatment. Unfortunately, the majority of patients diagnosed with PDAC are not candidates for surgical resection at time of diagnosis, and even those who undergo resection face a dismal 5-year survival rate of 10–20 %.[2–5] Many factors influence patient survival following pancreatectomy for PDAC, such as tumor size and grade, nodal metastases, lymphovascular invasion (LVI), perineural invasion (PNI), "T" stage and resection margin status.[6–14] Of these, only the extent of nodal harvest and resection margin can be influenced by the operating surgeon.

During pancreaticoduodenectomy (PD), the retroperitoneal (RP) margin, if taken correctly, has a finite extent along the superior mesenteric artery[13], whereas the pancreatic neck margin can be extended if intraoperative frozen section (FS) analysis demonstrates tumor involvement. It is routine practice for surgeons to obtain FS analysis of the pancreatic neck to evaluate the completeness of resection; if positive, this margin is usually addressed by additional parenchymal neck resection to achieve a clear margin. The status of the transected margin has been shown to be an important prognostic factor in PDAC.[15] Although it would seem a reasonable oncologic assumption that an R0, or microscopically negative

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margin at the pancreatic neck results in longer overall survival (OS), the available data for survival outcomes with regards to "R" status are inconclusive.[8,12,13,16,17] Schmidt et al.[16] found that treatment of patients with an isolated positive neck margin by subsequent total pancreatectomy was associated with an improvement in survival. Fatima et al.[8] also showed that R0 status, whether by initial en bloc resection or by re-excision of initially positive margins, led to similar improved long-term survival. By contrast, two studies demonstrated that although FS margin analysis increases the likelihood of achieving R0 resections, extending the pancreatic neck resection does not improve survival.[7,12] Other factors, such as tumor size, grade, and nodal metastasis impact survival after pancreatic resection, suggesting that determinants of tumor biology may be more critical than surgical maneuvers.[7,12,13,18] Extension of the pancreatic neck resection to achieve a microscopically negative margin with subsequent survival benefit therefore remains controversial.

The purposes of this study were to evaluate the determinants of a positive FS neck margin during PD for PDAC, to assess the association between a positive FS neck margin and OS for these patients, and to determine if conversion of a positive FS to a negative final margin by additional pancreatic resection is associated with improved OS.

METHODS

This retrospective study was conducted with Institutional Review Board (IRB00061992) approval.

Study Population

All patients who underwent PD for PDAC from January 2000 to August 2012 were identified retrospectively from a prospectively maintained database. Of these, all patients who had FS neck margins sent for pathologic review were included in this study. Patients undergoing PD for any other pathologic diagnoses were excluded from analysis.

Study Variables

Variables assessed included: demographic data, such as age, gender, and race; peritreatment characteristics, such as operation type (pylorus-preserving PD vs standard PD), portal vein (PV) and/or superior mesenteric vein (SMV) resection, length of hospital stay (LOS), 30-day mortality, and neoadjuvant and adjuvant chemotherapy and/or radiotherapy (CRT). Tumor characteristics, including histologic grade, tumor size, neck margin status on FS and PS, RP margin status on PS, the presence of LVI or PNI, nodal status, and "T" stage (as per AJCC 7), were recorded after a detailed review of pathology reports.

FS during PD was routinely obtained at the pancreatic neck and bile duct margins. Margins were taken en face and analyzed on both FS and permanent section (PS). If a positive margin was identified at the pancreatic neck, the decision of whether or not to extend the parenchymal neck resection was made by the attending surgeon. All margins were evaluated on PS. The RP margin was inked, cut into 3-mm sections, and submitted in entirety for PS analysis.

R0 neck margin was defined as macroscopic and microscopic absence of tumor cells at the neck margin. R1 was defined as microscopic presence of tumor cells and R2 as macroscopic presence of tumor at the neck margin. At our institution the CAP (College of American Pathologists) guidelines are used per the AJCC/UICC protocol: according to which, if tumor cells involve the margin then it is called R1 otherwise it is R0 (i.e., 0 mm distance of clearance of invasive carcinoma) and the distance of invasive carcinoma closest to the margin is recorded separately. Hence, even if the invasive carcinoma was within 1 or 2 mm of the neck and/or RP margin it was classified as "R0." The closest distance of the tumor cells to any margin (neck, RP) was recorded in the more recent path reports. The distance of tumor cells from the neck margin was not taken into account for this particular study, because many pathology reports before the initiation of this protocol did not record the closest distance of tumor cells from the margin. OS was calculated from the operative date to the date of last available follow-up or death. Survival data were gathered from medical records and through the Social Security Death Index.

Subgroups of patients were created to match the goals of our study. First, on the basis of the FS results, patients were divided into two groups: FS: Positive and FS: Negative, in order to analyze the role of FS neck margin status. Second, a separate subset analysis was done based on the PS neck margin status. Patients were divided into three groups for analysis: Group I (R0), Group II (R1 converted to R0, i.e., patients who had a positive FS neck margin and underwent additional neck resection to achieve negative margin on PS), and Group III (R1 with or without additional resection, i.e., all patients who had a positive neck margin on PS) (Fig. 1).

The primary objective was to identify factors associated with a positive FS neck margin and to evaluate the association between a positive FS neck margin and OS. The secondary objective was to evaluate if conversion of a positive FS neck margin to an R0 margin via additional parenchymal resection was associated with improved survival.

Statistical Analysis

Data were analyzed using SPSS version 19.0 (SPSS, Inc., Chicago, IL). Statistical comparison of means was

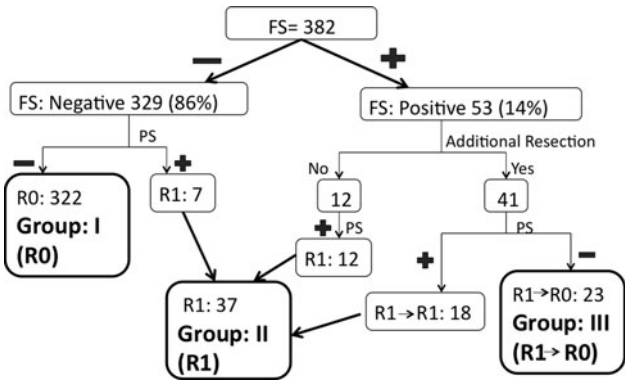

FIG. 1 Division of groups based on neck margin frozen and permanent sections

conducted for continuous variables using Student's *t* test or ANOVA as appropriate. Pearson chi-square tests were used to compare categorical variables. Kaplan–Meier log-rank survival analysis was used to determine the association of each pathologic factor on OS. Multivariate analysis was performed by including variables with $p \leq 0.1$ on univariate analysis, and results were expressed as hazard ratios (HR) and 95 % confidence intervals (CI). Statistical significance was predefined as $p \leq 0.05$.

RESULTS

Population Characteristics

A total of 396 patients underwent PD for PDAC of the pancreatic head and/or neck at Emory University Hospital between January 2000 and August 2012. Of these, 382 patients had FS neck margins assessed. One patient who underwent an R2 resection was excluded from the study. The demographic and perioperative characteristics of these 382 patients are summarized in Table 1a. Median age was 66 years (range, 36–88 years), and 50 % were females. Sixty-one patients (16 %) required PV and/or SMV resection. The median LOS was 10 days, and the 30-day mortality was 1.8 %. Only 19 (5 %) patients received neoadjuvant CRT, whereas 275 (72 %) underwent adjuvant CRT. The median OS was 15.5 months in the entire cohort.

Frozen Section Neck Margin and Associated Pathologic Factors

On FS, 329 patients (86 %) had a negative FS and 53 patients (14 %) had a positive FS neck margin. Patients with a positive FS neck margin had decreased OS compared with negative FS (11.1 vs. 17.3 months, $p = 0.013$, Fig. 2), regardless of margin status on final PS analysis. On univariate analysis (Table 2a), larger tumor size (3.65 cm vs. 3.2 cm, $p = 0.016$), presence of LVI (60 vs. 47 %, $p = 0.048$), and need for PV/SMV resection (26 vs. 14 %, $p = 0.042$) were significantly associated with a positive FS neck margin. On multivariate analysis (Table 2b) after accounting for histologic grade, tumor size, LVI, and PV/SMV resection, only larger tumor size remained independently associated with a positive FS neck margin (HR = 1.38, 95 % CI 1.06–1.78, $p = 0.014$).

Factors Associated with Decreased Survival

Univariate analysis for pathologic factors associated with OS (Table 3) showed poor histologic grade ($p = 0.005$), larger tumor size ($p < 0.001$), positive FS neck margin ($p = 0.014$), positive RP margin ($p = 0.003$), and higher "T" stage ($p = 0.022$) were significantly associated with decreased OS. On multivariate cox-regression analysis (Table 3) poor histologic grade (HR = 1.68, 95 % CI 1.15–2.45, $p = 0.007$), tumor size (HR = 1.23, 95 % CI 1.07–1.41, $p = 0.003$) and a positive RP margin (HR = 1.87, 95 % CI 1.17–2.98, $p = 0.009$) remained independently associated with decreased OS. A positive FS neck margin was not an independent prognostic factor of decreased OS on multivariate analysis.

Assessment of Survival Advantage After Converting a Positive FS Neck Margin

A separate subset analysis was performed based on PS neck margin status to evaluate the survival advantage of converting a positive FS neck margin to a negative margin on PS via additional resection. Of the 53 patients with a positive FS neck margin, 41 underwent additional resection to attempt clearance of the neck margin. Twenty-three (56 %) of those 41 patients were converted to R0. The 12 patients who did not undergo additional resection remained R1 on PS. Hence, we designated the 322 patients (84 %) who had an initial R0 neck margin as Group I, the 23 patients (6 %) with a positive FS who underwent additional neck resection to achieve R0 resection on PS as Group II (R1 → R0), and the 37 patients (10 %) who had an R1 neck margin on PS with or without additional resection as Group III.

The median OS in Group I (R0) was 17.3 months compared with 11.3 months in Group II (R1 → R0) and 11.1 months in Group III (R1, $p = 0.04$), suggesting that no survival advantage was gained by extending the pancreatic neck resection to achieve R0 status (Table 1a; Fig. 3).

Comparison of Groups I, II, and III

The distribution of demographic and perioperative characteristics among the three groups (Table 1a) was similar ($p =$ not significant). All 19 patients who received

TABLE 1 Clinicopathologic characteristics of groups I, II, and III

Variable	Total (%)	Group I (R0) *N* (%)	Group II (R1 ≥ R0) *N* (%)	Group III (R1) *N* (%)	*p* value[#]
a Patient and treatment factors					
n (%)[a]	382	322 (84)	23 (6)	37 (10)	
Median age (year)	66 (36–88)	66 (36–88)	65 (51–79)	70 (45–81)	0.355
Sex (female)	191 (50)	164 (51)	11 (48)	16 (43)	0.66
Race					0.736
White	290 (76)	239 (74)	20 (87)	31 (84)	
Black	70 (18)	63 (19)	2 (9)	5 (13)	
Other	21 (5)	19 (6)	1 (4)	1 (3)	
Operation type					
PPPD	250 (65)	213 (66)	18 (78)	19 (51)	0.082
SPD	132 (35)	109 (34)	5 (22)	18 (49)	
PV/SMV resection	61 (16)	46 (14)	5 (22)	10 (27)	0.099
LOS (days)	10 (4–74)	10 (4–74)	10 (5–56)	11 (4–38)	0.493
30-day mortality	7 (1.8)	4 (1.2)	1 (4.3)	2 (5.4)	0.131
Neoadjuvant CRT	19 (5)	19 (6)	0 (0)	0 (0)	0.16
Adjuvant CRT	275 (72)	232 (72)	17 (74)	26 (70)	0.953
OS (mo)	15.5	17.3	11.3	11.1	**0.039**
b Pathologic factors					
Histologic grade					
Well	34 (9)	30 (9)	2 (9)	2 (5)	0.947
Moderate	251 (66)	211 (65)	16 (69)	24 (65)	
Poor	94 (25)	78 (24)	5 (22)	11 (30)	
Tumor size (cm)	3.1 (0.6–8)	3.0 (0.7–8)	3.3 (1.5–5)	4.0 (0.6–6.2)	**0.028**
RP margin (+)	60 (16)	50 (15)	1 (4)	9 (24)	0.127
LN (+)	253 (66)	211 (65)	20 (87)	22 (59)	0.074
RP margin/LN (+)	265 (69)	220 (68)	20 (87)	25 (67)	0.177
LVI	187 (49)	151 (47)	13 (56)	23 (62)	0.089
PNI	331 (87)	276 (86)	22 (96)	33 (89)	0.526
T stage					
Tx	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0.479
T1	21 (5)	18 (5)	1 (4)	2 (5)	
T2	45 (12)	37 (11)	3 (13)	5 (13)	
T3	291 (76)	249 (77)	18 (78)	24 (65)	
T4	24 (6)	17 (5)	1 (4)	6 (16)	

[a] (%) Relative to total cases ($n = 382$)

p value for Groups I, II, and III

PPPD pylorus-preserving pancreaticoduodenectomy, *SPD* standard pancreaticoduodenectomy, *PV* portal vein, *SMV* superior mesenteric vein, *LOS* length of stay, *CRT* chemoradiation therapy, *OS* overall survival, *RP* retroperitoneal, *LN* lymph node, *LVI* lymphovascular invasion, *PNI* perineural invasion

neoadjuvant therapy (CRT) were in Group I (R0 resections) (6 vs. 0 and 0 %, $p = 0.16$). Patients who underwent adjuvant CRT were equally distributed among all three groups ($p = 0.953$).

Pathologic characteristics (Table 1b) were similar among the three groups, with the exception of median tumor size, which measured 3.0 cm in Group I, 3.3 cm in Group II, and 4.0 cm in Group III ($p = 0.028$). Although not reaching statistical significance, RP margin positivity and/or nodal metastasis was highest in Group II (87 %) compared with 68 and 67 % in Groups I and III, respectively ($p = 0.177$).

DISCUSSION

The purpose of this study was to evaluate the determinants of and the association with survival of a positive FS neck margin during PD for PDAC and to evaluate if converting a positive FS to a negative final margin is

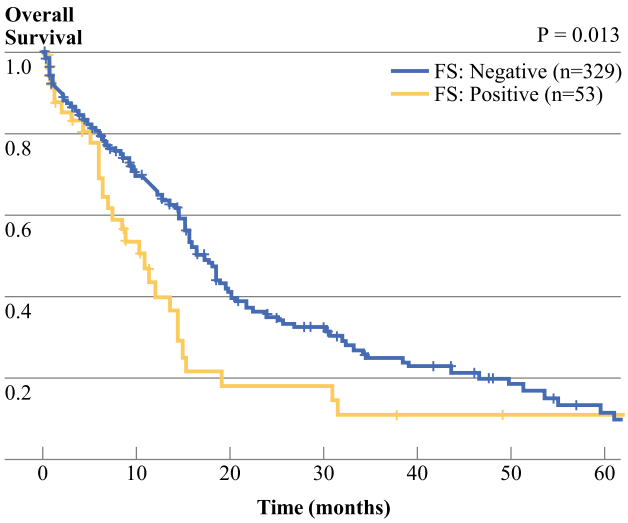

FIG. 2 Frozen section neck margin status and survival

associated with improved OS. We found that although patients with a positive FS neck margin have worse OS compared with those with a negative FS, a positive FS neck was not independently associated with decreased OS after accounting for other adverse pathologic factors. The subset of patients with a positive FS neck margin who achieved a negative neck margin on PS via additional resection did not show improved survival compared with those with positive neck margins on PS, thus raising the question of utility of FS neck margin assessment for these patients. The presence of tumor cells at the resection margins is likely to be a surrogate marker of aggressive tumor biology. Clearing the remnant microscopic tumor at the neck margin does not appear to influence the outcome in the presence of aggressive tumor biology.

In our study, only tumor size remained significantly associated with a positive FS on multivariate analysis. Histologic

TABLE 2 Univariate and multivariate analyses for factors associated with having a positive frozen section neck margin

a Univariate analysis

Variable	FS: Negative ($n = 329$) *N* (%)	FS: Positive ($n = 53$) *N* (%)	*p* value
Histologic Grade			0.067
Well	31 (9)	3 (6)	
Moderate	216 (66)	35 (66)	
Poor	79 (24)	15 (28)	
Tumor size (cm)	3.2	3.65	0.**016**
RP margin (+)	53 (16)	7 (13)	0.771
LN (+)	214 (65)	39 (73)	0.313
RP margin/LN (+)	224 (68)	41 (77)	0.254
LVI	155 (47)	32 (60)	**0.048**
PNI	283 (86)	48 (90)	0.783
T stage			
Tx	1 (0.3)	0 (0)	0.437
T1	18 (5)	3 (56)	
T2	37 (11)	8 (15)	
T3	255 (77)	36 (68)	
T4	18 (5)	6 (11)	
PV/SMV resection	47 (14)	14 (26)	**0.042**
OS (months)	17.3	11.1	**0.013**

b Multivariate analysis of factors associated with FS: Positive

Variable	Hazard ratio	95 % Confidence interval	*p* value
Histologic grade	1.3	0.62–2.73	0.751
Tumor size (cm)	1.38	1.06–1.78	**0.014**
LVI	1.83	0.88–3.79	0.102
PV/SMV resection	1.79	0.79–4.04	0.16

RP retroperitoneal, *LN* lymph node, *LVI* lymphovascular invasion, *PNI* perineural invasion, *PV* portal vein, *SMV* superior mesenteric vein, *OS* overall survival

TABLE 3 Univariate and multivariate analyses for pathologic factors associated with overall survival

		Univariate analysis			Multivariate analysis		
Variable	OS (months)	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Histologic grade		1.59	1.15–2.2	**0.005**	1.68	1.15–2.45	**0.007**
Well	51.32						
Moderate	15.85						
Poor	14.43						
Tumor size (cm)	-	1.25	1.11–1.39	**<0.001**	1.23	1.07–1.41	**0.003**
FS: Positive	11.14	1.63	1.1–2.4	**0.014**	1.29	0.79–2.13	0.311
RP margin (+)	11.47	1.74	1.21–2.51	**0.003**	1.87	1.17–2.98	**0.009**
LN (+)	15.02	1.33	0.97–1.82	0.072	1.51	0.42–5.34	0.526
LVI	15.2	1.37	0.97–1.92	0.074	1.22	0.83–1.81	0.313
PNI	15.22	1.42	0.82–2.45	0.212			
T Stage	-	1.3	1.04–1.64	**0.022**	1.04	0.77–1.41	0.811

HR hazard ratio, *CI* confidence interval, *RP* retroperitoneal, *LN* lymph node, *LVI* lymphovascular invasion, *PNI* perineural invasion, *OS* overall survival

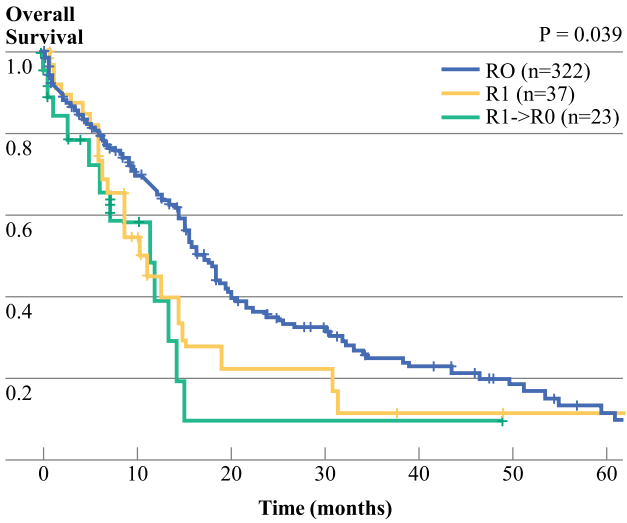

FIG. 3 Pancreatic neck margin status and survival

grade, tumor size, and RP margin positivity were independently associated with decreased OS, similar to previous studies.[7,9,19–22] FS neck margin status was not associated with OS on multivariate analysis, similar to that reported by Dillhoff et al.[7] All patients who received neoadjuvant CRT had an R0 neck margin, suggesting better locoregional control of the tumor.[23,24] In the FS: Positive neck margin group, the distribution of adverse pathologic factors: poor histologic grade, larger tumor size, RP margin positivity, LN positivity, LVI, PNI, and T4 stage was higher compared with the FS: Negative group (Table 2a). Similarly, the group with a final neck margin positive on PS (Group III) had a higher incidence of poor histologic grade, RP margin positivity, LVI, and more T4 tumors (Table 1b). These findings suggest that a positive neck margin may correlate with more aggressive tumor biology.[18]

The current study is unique because its focus is solely on the pancreatic neck margin, where additional parenchymal transection can be performed to obtain a clean pancreatic margin. Tumor infiltration at the transected margins has been associated with a worse outcome as compared to the involvement of the mobilized margin[25]; hence, we focused on the surgical outcomes of patients who underwent additional resection of the neck margin. Of the 53 initially positive FS neck margins, 23 patients who underwent additional resection were successfully converted to R0 margin on PS, with the anticipation that clearing residual disease might improve their survival. Hernandez et al.[12] looked at all surgically resected margins, including pancreatic neck, bile duct, PV/SMV, bowel, etc. They reported that patients who underwent additional resection had a similar outcome to those undergoing R1 resection (OS = 11 vs. 13 months) and a worse outcome than those who had R0 margin without additional resection (OS = 11 vs. 21 months, $p = 0.001$). Similarly, we found comparable survival in patients who achieved an R0 resection after additional neck margin resection after a positive FS versus patients with an R1 resection (11.3 vs. 11.1 months). The high rate of RP and/or LN positivity (87 %) and PNI (96 %) observed in Group II patients may have contributed to poor survival even after attaining an R0 neck margin.[13,26] These findings support the rationale that, in the presence of other aggressive tumor-related factors, obtaining a negative resection margin alone may not improve OS.

Our findings are in contrast to those of Fatima et al.[8] who showed that OS was similar between the patients who had an initial R0 resection or attained an R0 after reexcision of an initially positive margin compared with decreased OS in patients undergoing R1 resection. Their

study also incorporated the status of multiple surgically transected margins; therefore, the prognostic significance of neck margin status alone could not be ascertained. Schmidt et al.[16] reported that conversion of PD to total pancreatectomy (TP) in the case of a persistently positive neck/body margin provides a survival benefit, although this has not been adopted as standard practice. TP is associated with higher morbidity and mortality compared with PD.[22] All patients in the current study underwent a PD and if additional neck resection failed to clear the margin of a patient with an initial positive FS neck margin, the remnant tumor was left in situ. None of our patients underwent total TP to attain a negative neck margin.

This is a retrospective observational study and has the inherent accompanying biases. Larger multi-institutional studies need to be undertaken to further evaluate the prognostic significance of FS neck margin status. This large, single-institution study demonstrates that after considering adverse clinicopathologic factors, FS neck margin status is not associated with OS. A positive FS neck margin may be a surrogate for aggressive tumor biology. Converting a positive margin to a negative one via additional resection is not associated with improved survival. We feel that routine assessment of FS neck margins at the time of PD for PDAC may not be warranted. Further assessment of this question in a multicenter analysis may further our understanding of this issue.

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