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Effect of Neoadjuvant Chemoradiation and Surgical Technique on Recurrence of Localized Pancreatic Cancer

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Abstract
Objectives To determine the influence of neoadjuvant chemoradiation and standardized dissection of the superior mesenteric artery upon the oncologic outcome of patients with localized pancreatic adenocarcinoma.
Methods One hundred ninety-four patients with pancreatic adenocarcinoma who underwent pancreaticoduodenectomy between 2004 and 2008 were evaluated. The retroperitoneal dissection was performed directly along the superior mesenteric artery in all cases. A standard histopathologic protocol that measured the "superior mesenteric artery (SMA) margin distance" between cancer cells and the superior mesenteric artery was employed.
Results Seventy-six percent of patients received neoadjuvant chemoradiation. The SMA margin was positive in 4% of patients but an additional 22% of patients with a negative margin had a SMA margin distance of ≤1 mm. Preoperative CT images overestimated the SMA margin distance in 73% of cases. Patients who received chemoradiation had longer SMA margin distances than those who did not. Patients who received chemoradiation and had a SMA margin of >1 mm had the lowest recurrence rates. Administration of neoadjuvant chemoradiation and lower estimated blood loss were independently associated with longer progression-free survival on multivariate analysis.
Conclusions Preoperative chemoradiation and meticulous dissection of the superior mesenteric artery maximize the distance between cancer cells and the SMA margin and may influence locoregional control.

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Introduction

In a recent autopsy study, 80% of patients who had undergone resection for early stage pancreatic adenocarcinoma (PDAC) were found to have died with locally recurrent cancer.[1] The presumptive source of this recurrence is cancer cells left in situ following microscopically incomplete resection. For this reason, patients with adenocarcinomas of the rectum and esophagus—who, like patients with PDAC, have tumor anatomy and biology that put them at high risk for locoregional recurrence—are treated with multimodality approaches specifically designed to minimize the incidence of residual cancer cells at the surgical margins. Indeed, the administration of preoperative (neoadjuvant) chemoradiation,[2] the use of a standardized surgical procedure designed to maximize the distance between the primary cancer and the radial resection margin,[3] and standardized pathologic analysis of the oncologically critical margin[4] have helped to reduce rates of local recurrence among patients with rectal cancer to as low as 5%.[5]

Despite high rates of locoregional recurrence following pancreaticoduodenectomy either alone[6, 7] or followed by postoperative therapy,[8, 9] the critical components of therapy that have been shown to be effective at reducing locoregional recurrence among patients with rectal cancer are not uniformly applied to patients with localized PDAC. The administration of neoadjuvant chemoradiation to such patients is not routine in most treatment centers. Moreover, the critical steps in performing pancreaticoduodenectomy are not standardized, even among high-volume pancreatic surgeons. Finally, protocols used to guide histopathologic evaluation of pancreaticoduodenectomy specimens have not been uniformly adopted.[10] We have hypothesized that failure to implement these strategies has contributed to the ongoing problem of locoregional cancer recurrence among patients with localized PDAC.

At our institution, routine care of patients with localized PDAC includes preoperative delivery of external-beam radiation with concurrent chemotherapy followed by a standardized technical operation.[11–16] Because the superior mesenteric artery (SMA) margin is the margin most frequently found to be positive for cancer cells following pancreaticoduodenectomy, the SMA is meticulously dissected from the uncinate process to remove all soft tissue to the right of the artery, and to maximize the distance between microscopic cancer cells and the cut margin that lies directly along this vessel (hereafter referred to as the "SMA margin distance" (Fig. 1)).[10, 17] After surgery, all specimens are analyzed using a standardized histopathologic protocol that includes microscopic measurement of the SMA margin distance. The favorable clinical outcomes associated with this strategy,[18] combined with the theoretic ability of preoperative chemoradiation to sterilize the surgical margins in patients with solid tumors,[19] has prompted us to broaden its application to include patients with borderline-resectable primary pancreatic cancers that abut the SMA or celiac axis.[13]

Because the administration of neoadjuvant chemoradiation and the performance of surgery with meticulous, standardized dissection of the SMA are not routine, the influence of their incorporation into multimodality treatment strategies upon the oncologic outcome of patients with potentially and borderline resectable has not been established. In this study, we critically examined the associations between chemoradiation, the SMA margin distance, locoregional control, and overall survival (OS) in patients with localized PDAC who underwent potentially curative resection.

Patients and Methods

The University of Texas MD Anderson Cancer Center Institutional Review Board granted approval for this

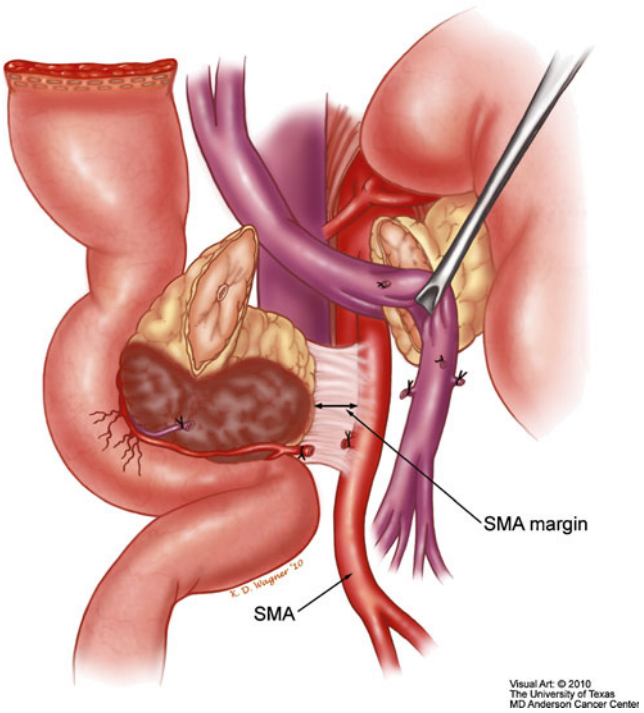

Fig. 1 Diagram showing anatomy of the superior mesenteric artery (*SMA*) margin. In all cases, the SMA margin was dissected directly along the periadventitial plane of the SMA. The distance between the primary cancer and inked SMA margin was measured microscopically

retrospective study. We retrieved clinical data on all patients who underwent pancreaticoduodenectomy for PDAC between 2004 and 2008 from our prospectively maintained, institutional pancreatic tumor database.[20] We excluded from analysis patients with a final diagnosis of invasive adenocarcinoma arising in an intraductal papillary mucinous neoplasm, mucinous cystadenocarcinoma, or any other nonpancreatic periampullary adenocarcinoma.

Radiographic Staging

Multidetector computed tomography (CT) using a 16- or 64-detector row scanner (General Electric Medical Systems, Milwaukee, WI) was routinely performed both prior to neoadjuvant therapy (if applicable) and immediately prior to surgery at our institution. A standard protocol optimized for imaging pancreatic tumors was used in all cases. Oral contrast material was administered 90–120 min prior to imaging. Following injection of 120–150 mL of iodinated contrast at a rate of 4–5 mL/s, dual-phase imaging was performed. The pancreatic parenchymal phase was obtained 35–40 s after the start of the contrast injection, and the portal venous phase was obtained 50–70 s after the start of the contrast injection. Images were transferred to a Picture Archiving and Communications System (iSite; Stentor, Brisbane, CA), and they were then reconstructed at either 0.625- or 1.25-mm slice thickness for analysis. We used multiplanar reconstructions as necessary to clarify vascular anatomy.

Potentially resectable PDAC was defined by (1) the absence of extrapancreatic disease; (2) no evidence of tumor extension to the SMA, celiac axis, or hepatic artery; and (3) a patent superior mesenteric (SMV)–portal vein (PV) confluence on CT images.[21] Anatomically defined borderline resectable cancers were those that demonstrated tumor abutment (180° or less of the circumference of the vessel) of the SMA or celiac axis; abutment or encasement (>180° of the circumference of the vessel) of a short segment of the hepatic artery; or short-segment occlusion of the superior mesenteric vein (SMV), PV, or SMV-PV confluence that was amenable to vascular resection and reconstruction.[13, 22]

Treatment Sequencing

Most patients with potentially resectable PDAC and all patients with borderline resectable PDAC underwent neoadjuvant chemoradiation prior to surgery. Patients received external-beam radiation (typically to 30 or 50.4 Gy) with concurrent gemcitabine, 5-FU or capecitabine. Gemcitabine-based, systemic chemotherapy was delivered prior to chemoradiation in selected cases. Upon completion of neoadjuvant treatment, patients were restaged. Patients who had a sufficient performance status for major abdominal surgery and who did not have radiographic evidence of disease progression were brought to the operating room for planned pancreaticoduodenectomy. Patients who underwent initial surgery were most often those who chose this treatment sequence but also were those in whom a cytologic diagnosis of malignancy could not be confirmed preoperatively and those in whom preoperative chemoradiation could not be delivered effectively. Most patients in the surgery-first group underwent postoperative adjuvant therapy.[23]

Standard Surgical Technique

Pancreaticoduodenectomy was performed using a standardized technique[24] and surgical margins were designated in accordance with the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[25, 26] In every case, the SMV was completely mobilized to expose the proximal SMA. Dissection of the uncinate process from the retroperitoneum was then performed directly along the periadventitial plane of the SMA, from the first jejunal branch of the SMV to the takeoff of the SMA from the aorta, to remove all the soft tissue to the right of the SMA and thereby maximize the SMA margin distance.[10, 17] Controlled tangential or segmental resection of the SMV, PV, or SMV-PV confluence was performed when the operating surgeon could not separate the pancreatic head or the uncinate process from these vessels.[27]

Histopathologic Evaluation of Surgical Specimens

Histopathologic evaluation of the surgical specimen was performed using a standardized protocol per AJCC guidelines[26] that included assessment of the SMA, common bile duct, and pancreatic neck margins. The surgeon and pathologist inked the SMA margin immediately following removal of the specimen. The entire inked SMA margin was submitted perpendicularly for microscopic evaluation after overnight fixation in 10% buffered formalin. The closest microscopic distance, to the nearest millimeter, between cancer cells and the SMA margin was microscopically measured and prospectively recorded. The specimen was designated R_0 if no tumor cells were identified at any of the resection margins, and as R_1 if cancer cells were present at any margin. The grade of neoadjuvant chemoradiation treatment effect was assessed on permanent sections and scored using a previously published grading scheme.[11]

Concordance of Radiographic and Pathologic Measurements of SMA Margin Distance

Two faculty gastrointestinal radiologists (A.B. and P.B.) who were blinded to all other clinical data re-reviewed all

preoperative CT scans for this study to identify the shortest distance from the primary tumor to the SMA. This distance was measured on transverse images and recorded to the nearest millimeter. When the tumor was located in the superior aspect of the head of the pancreas, the shortest oblique measurement was recorded. When the SMA margin distance measured <1 cm (as determined by pathology), we assessed agreement between the pathologic and radiologic measurements of the SMA margin distance using a concordance correlation coefficient. We classified concordance as follows, >0.8, almost perfect agreement; 0.6–0.8, substantial agreement; 0.4–0.6, moderate agreement; and <0.4, poor agreement.[28]

Follow-up and Definitions of Recurrence

After surgery, patients were evaluated every 4 months with a physical examination, chest radiography, and abdominal CT. For patients with no evidence of disease after 2 years of follow-up, evaluations were reduced to 6-month intervals. The development of a new low-density mass or abnormal lymphadenopathy in the region of the resected pancreas or mesenteric root was considered locoregional recurrence in this study. Three patients believed to have developed second primary cancers of the pancreas following resection were reported as having local recurrence. Radiographic evidence of a low-density mass in the liver or lungs or new-onset ascites was considered evidence for distant recurrence. Biopsy of recurrence was rarely performed. Only the first site(s) of recurrent disease was documented for this study.

Statistical Analysis

We defined OS as the time interval between the date of histopathologic diagnosis and the date of death from any cause. Patients who were alive at the last follow-up date were censored at that time. We defined progression-free survival (PFS) as the time interval between the date of histopathologic diagnosis and the date of first recurrence or death, whichever occurred first; we censored patients who were alive without disease recurrence at the last follow-up date. Similarly, we defined local progression-free survival (LPFS) as the time interval between the date of histopathologic diagnosis and the date of first locoregional recurrence or death, whichever occurred first; we censored patients who were alive without locoregional recurrence at the last follow-up date. We used the Kaplan–Meier method to estimate OS, PFS, and LPFS probabilities, and we used the log-rank test to assess differences among subgroups of patients. We fit Cox proportional hazards regression models to assess associations between patient characteristics, disease, and treatment and OS, PFS, and LPFS. All statistical tests were two-tailed, and p values of <0.05 were deemed statistically significant. We used SAS (version 9.0; SAS Institute, Inc., Cary, NC) and S+ (version 8.0; Insightful Corp, Seattle, WA) for all statistical analyses.

Results

Demographic and Treatment Characteristics

The clinicopathologic and treatment characteristics of all 194 patients who underwent pancreaticoduodenectomy for biopsy-proven PDAC during the period studied are reported in Table 1. One hundred forty-seven patients (76%) received neoadjuvant chemoradiation with concurrent gemcitabine (n=81) or 5-fluorouracil or capecitabine (n=64). External-beam radiation was delivered at a total dose of 30 Gy (15 2.0-Gy fractions, n=57) or greater (typically 50.4 Gy in 28 2.8-Gy fractions, n=88). The specific chemoradiation regimen administered to two patients was not recorded. The primary reason given for not administering chemoradiation preoperatively in patients who did not receive it included choice (n=28), a failure to secure a tissue diagnosis (n=7), a preoperative assumption of an alternate histopathologic diagnosis (n=4), or other reasons such as a perceived inability to deliver preoperative therapy effectively (n=8).

The demographic characteristics of patients who received neoadjuvant chemoradiation were similar to the characteristics of those who did not (p>0.05). Patients with borderline resectable disease were preferentially treated with chemoradiation. Of 152 (78%) patients with potentially resectable PDAC upon presentation, 57 (38%) received both preoperative systemic chemotherapy and chemoradiation, 49 (32%) received chemoradiation alone, and two (1%) received chemotherapy alone. All 41 patients with borderline resectable tumors were treated with preoperative chemoradiation; 31 (76%) of these received systemic chemotherapy as well. One patient who initially presented with locally advanced disease secondary to radiographic findings consistent with SMA encasement was treated with systemic chemotherapy alone prior to surgery.

Although patients treated with preoperative chemoradiation had more advanced disease upon presentation than those who underwent surgery first, the rate of vascular resection was similar in the two groups (p=0.14). Estimated blood loss (EBL) was greater in patients who received chemoradiation than in those who did not (p=0.02).

Pathologic Characteristics

Following resection, the median tumor diameter (p=0.03) and the percentage of patients with positive lymph nodes (p< 0.001) were both smaller in the group that received chemoradiation than in the group that did not (Table 1). However,

Table 1 Clinicopathologic and treatment characteristics of 194 patients who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma, 2004–2008, at The University of Texas MD Anderson Cancer Center

Variable	Total (*N* (%))	Preoperative CXRT (*n* (%))	Initial surgery (*n* (%))	*p*
All patients	194	147 (76)	47 (24)	
Demographics				
Sex		0.7		
Male	103 (53)	79 (54)	24 (51)	
Female	91 (47)	68 (46)	23 (49)	
Median (range) age (years)	64.9 (24.9–85.4)	64.8 (34.5–85.4)	65.1 (24.9–84.5)	0.88
Pretreatment stage				NA[a]
Potentially resectable	152 (78)	106 (72)	46 (98)	
Borderline resectable	41 (21)	41 (28)	0	
Locally advanced	1 (1)	0	1 (2)	
Treatment				
Vascular resection				0.14
Yes	71 (37)	58 (39)	13 (28)	
No	123 (63)	89 (61)	34 (72)	
Median (range) EBL (mL)	700 (90–4,700)	700 (90–4,700)	500 (100–2,500)	0.02
Final pathology				
Median (range) tumor diameter (cm)	2.5 (0.3–8.0)	2.4 (0.3–8.0)	3.0 (1.3–5.5)	0.03
Grade				0.35
Well differentiated	4 (2)	2 (2)	2 (4)	
Moderately differentiated	149 (77)	110 (75)	39 (83)	
Poorly differentiated	33 (17)	27 (18)	6 (13)	
Not evaluable	3 (1)	3 (2)	0	
Not evaluated	5 (3)	5 (3)	0	
Margin (*R*) status				0.14
R_0	179 (92)	138 (94)	41 (87)	
R_1	15 (8)	9 (6)	6 (13)	
Lymph node (*N*) status				<0.001
N_0	78 (40)	72 (49)	6 (13)	
N_1	116 (60)	75 (51)	41 (87)	
Treatment effect grade				NA
I	1 (1)	1 (1)	NA	
IIa	63 (32)	63 (43)	NA	
IIb	59 (30)	59 (40)	NA	
III	18 (9)	18 (12)	NA	
IV	3 (1)	3 (2)	NA	
Not evaluated	3 (1)	3 (2)	NA	

CXRT chemoradiation therapy, *EBL* estimated blood loss

[a] Patients with borderline resectable disease received neoadjuvant chemoradiation routinely

the overall rate of R_0 resection did not differ based upon preoperative chemoradiation status (p=0.14). Among 15 (8%) patients who underwent an R_1 resection, the SMA margin was positive in eight, the pancreatic neck margin was positive in six, and the common bile duct margin was positive in three.

The SMA margin distances of patients stratified by pretreatment stage and preoperative chemoradiation status are reported in Table 2. All eight positive SMA margins were found in patients with potentially resectable primary cancers. Of these patients, five did not receive preoperative chemoradiation (p=0.016, Fisher's exact test). Among 178 patients with a negative SMA margin in whom the SMA distance was recorded, 40 (22%) had a margin distance of ≤1 mm. Overall, the distribution of SMA margin distances of patients with potentially resectable cancers was similar to the distribution of margin distances in those with more advanced tumors (p=0.48). However, patients who received chemoradiation had longer SMA margin distances than those who did not (p=0.01).

Table 2 Superior mesenteric artery (SMA) margin distance measured histopathologically following pancreaticoduodenectomy, stratified by pretreatment disease stage and preoperative chemoradiation (CXRT) status

Pretreatment stage				Preoperative chemoradiation status		
SMA margin distance	Potentially resectable (*n* (%))	Borderline or locally advanced (*n* (%))	p^a	Preoperative CXRT (*n* (%))	Initial surgery (*n* (%))	p^a
Total patients	152	42	0.48	147	47	0.01
Positive	8 (5)	0		3 (2)	5 (11)	
≤1 mm	33 (22)	7 (17)		28 (19)	12 (26)	
>1 mm<1 cm	53 (35)	19 (46)		53 (36)	19 (40)	
≥1 cm	52 (34)	14 (34)		57 (39)	9 (19)	
Missing	6 (4)	2 (5)		6 (4)	2 (4)	

[a] *p* refers to overall comparison between treatment groups

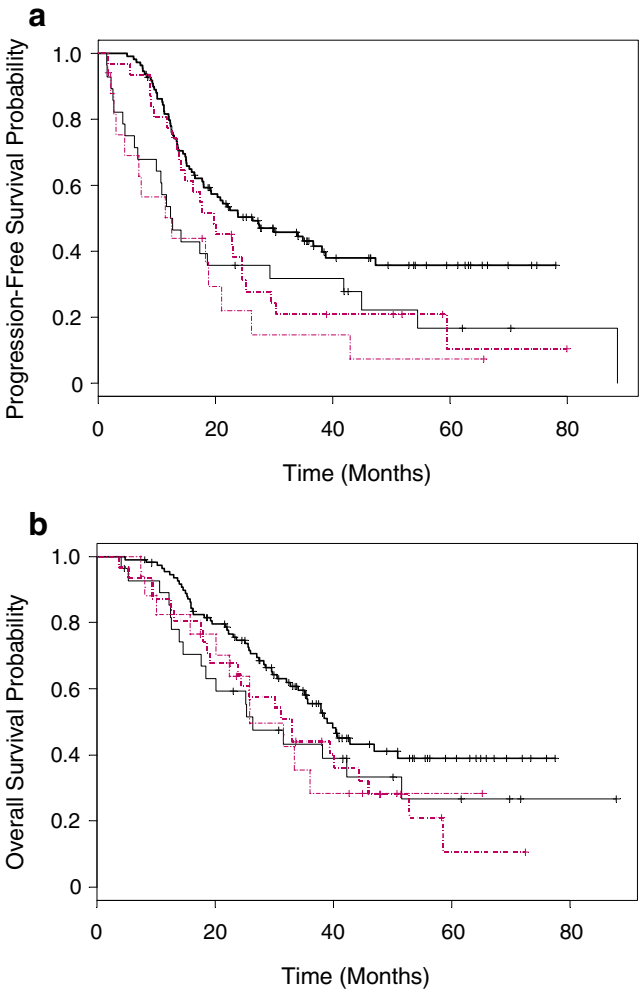

Fig. 2 Kaplan–Meier analysis of **a** progression-free survival and **b** overall survival of patients stratified by chemoradiation and superior mesenteric artery (*SMA*) margin distance. *Thick black line*, chemoradiation and SMA distance of >1 mm; *thick red line*, chemoradiation and SMA margin positive or distance of ≤1 mm; *thin black line*, initial surgery and SMA margin distance of >1 mm; *thin red line*, initial surgery and SMA margin positive or distance of ≤1 mm

Time to Cancer Progression

The median follow-up for all patients was 30 months, and the median follow-up of patients still alive was 42 months. At last follow-up, 131 (68%) patients had died or developed recurrent disease. The median PFS of all patients was 19.5 (95% confidence interval (CI), 17.2–24.4) months. Longer PFS (p=0.003; Fig. 2a) and LPFS (p=0.01) were both associated with the administration of preoperative chemoradiation and longer SMA margin distance. Patients who received chemoradiation and had a histopathologically measured SMA margin distance of >1 mm had the most favorable PFS (26 (95% CI, 14.6–37.6) months) and LPFS (29.7 (95% CI, 17.3–42.2) months).

Pattern of Recurrence

At last follow-up, among patients in whom the SMA margin distance was measured (n=186), isolated locoregional recurrence was identified in 26 (14%) patients and isolated distant recurrence at one or more sites was identified in 67 (36%) patients. Concurrent locoregional and distant recurrence was identified in 16 (9%) patients. The rates of recurrence stratified by chemoradiation and SMA margin distance are reported in Table 3. Patients who underwent initial surgery and had a measured SMA margin distance of ≤1 mm had the highest rates of overall (82%), locoregional (36%), and distant (59%) recurrence.

Overall Survival

The median OS of all 194 patients was 35.6 (95% CI, 30.5–40.7) months. The Kaplan–Meier OS curves of subgroups of patients stratified by preoperative chemoradiation and SMA margin distance were statistically similar (p=0.15; Fig. 2b), although patients who received preoperative chemoradiation and had a SMA margin distance of >1 mm

Table 3 Disease recurrence by preoperative chemoradiation (CXRT) status and superior mesenteric artery (SMA) margin distance, for patients in whom SMA margin distance was measured (n=186)

Preoperative CXRT	SMA margin distance	Patients (n)	Recurrences (n (%))	Locoregional recurrences (n (%))	Distant recurrences (n (%))	Concurrent recurrences (n (%))
Yes	>1 mm	110	54 (49)	13 (12)	32 (29)	9 (8)
Yes	Positive or ≤1 mm	31	21 (68)	5 (16)	15 (48)	1 (3)
No	>1 mm	28	20 (71)	4 (14)	12 (43)	4 (14)
No	Positive or ≤1 mm	17	14 (82)	4 (24)	8 (47)	2 (12)

had the longest median OS (39.5 (95% CI, 33.6–44.4) months).

Multivariate Survival Analyses

We constructed Cox proportional hazards models for LPFS, PFS, and OS that included potential covariates that we felt were clinically relevant based on our literature review and clinical experience. These included age, EBL, vascular resection, tumor size, tumor grade, node status, SMA margin distance (>1 mm vs. ≤1 mm or positive), and neoadjuvant chemoradiation. Age, vascular resection, tumor size, tumor grade, and node status were not associated with LPFS, PFS, or OS (data not shown). Lower EBL and administration of neoadjuvant chemoradiation were independently associated with a longer LPFS and PFS but only EBL was independently associated with longer OS (Table 4). After adjustment for the effects of potential covariates, SMA margin distance was not significantly associated with any of these outcome metrics (Table 4).

Radiographic and Pathologic Correlation

To evaluate clinicians' ability to predict the histopathologic status of the SMA margin following a standard technical operation using preoperative cross-sectional imaging, we compared the SMA margin distance measured using preoperative CT with that measured histopathologically in the surgical specimen (Fig. 3). The relationship between these measures is graphically depicted in Fig. 4. Of eight patients in whom the SMA margin was R_1 as determined microscopically, we estimated by CT that six of them would have had R_0 margins, with SMA margin distances of 3–18 mm. In all, CT overestimated the distance between the primary cancer and the SMA in 88 (73%) of 120 cases evaluated. The concordance correlation coefficient between the two measures was 0.07 (95% CI, 0.02–0.13). Among patients who did not receive neoadjuvant chemoradiation, the concordance correlation coefficient was 0.24 (95% CI, 0.07–0.39).

Discussion

A close radial resection margin is a known risk for local recurrence and death in cancers of the rectum and esophagus.[29, 30] Multimodal treatment strategies for these cancers now include preoperative chemoradiation and meticulous surgical technique with attention to the radial resection margin to reduce rates of locoregional recurrence and to prolong survival. We performed this analysis to rigorously explore the relationships between surgical

Table 4 Multivariate Cox proportional hazards model for LPFS, PFS and OS

Covariate	Coefficient	SE	Hazard ratio	p value
LPFS				
EBL[a]	0.45	0.14	1.57	0.001
Neoadjuvant chemoradiation=yes (vs. no)	−0.58	0.22	0.56	0.007
SMA margin distance>1 mm (vs. ≤1 mm or positive)	−0.24	0.21	0.79	0.26
PFS				
EBL[a]	0.35	0.13	1.41	0.008
Neoadjuvant chemoradiation=yes (vs. no)	−0.61	0.20	0.54	0.003
SMA margin distance>1 mm (vs. ≤1 mm or positive)	−0.27	0.20	0.76	0.17
OS				
EBL[a]	0.54	0.14	1.71	0.0001
Neoadjuvant chemoradiation=yes (vs. no)	−0.40	0.23	0.67	0.08
SMA margin distance>1 mm (vs. ≤1 mm or positive)	−0.13	0.22	0.88	0.54

LPFS local progression-free survival, *EBL* estimated blood loss, *SMA* superior mesenteric artery, *PFS* progression-free survival, *OS* overall survival

[a]Transformed as log(EBL)

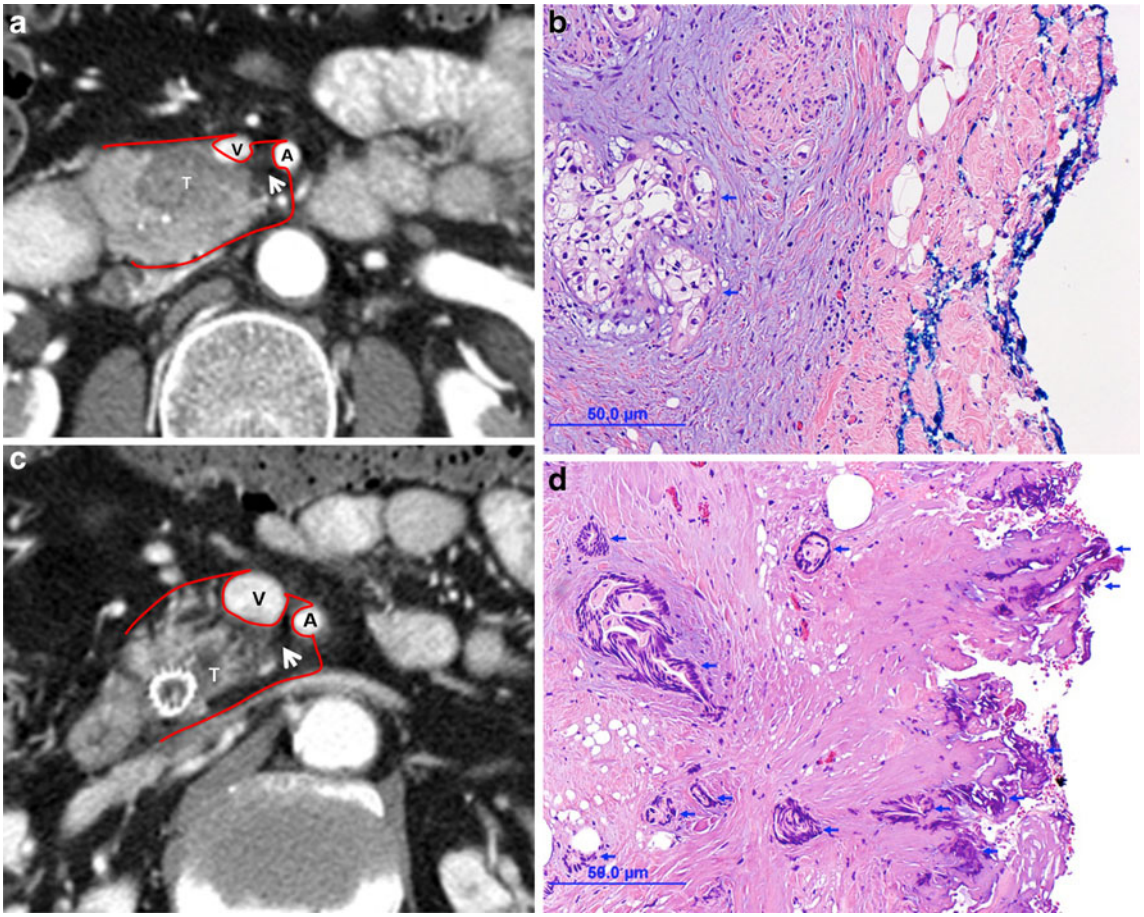

Fig. 3 Superior mesenteric artery (*SMA*) margin distance estimated radiographically and measured histopathologically in two patients with a substantial mesopancreatic fat plane (*arrow*) between the primary cancer (*T*) and SMA (*A*) on preoperative CT imaging. *Red line* depicts the path of surgical resection performed as part of total mesopancreas excision. *V* SMV. **a**, **b** A patient with a negative SMA margin but tumor cells (*arrows*) within 1 mm of the inked margin. Tangential resection with saphenous vein reconstruction of the SMV-PV was performed as part of the procedure. **c**, **d** A patient with a positive SMA margin. Preoperative imaging typically overestimated the SMA margin distance

technique, preoperative chemoradiation, and cancer-related outcomes in patients with PDAC. By examining radiographic, surgical, and histopathologic parameters, we demonstrated that both neoadjuvant chemoradiation and the routine use of meticulous surgical technique with strict attention to the SMA margin maximize the distance between cancer and this oncologically critical margin. Strategies that incorporate these clinical components may contribute to locoregional control following surgery in patients with localized cancers.

The SMA margin is the margin most frequently found to be positive for cancer cells following resection of PDAC.[10, 16, 17] The margin is defined by the AJCC as the soft tissue margin directly adjacent to the proximal 3–4 cm of the SMA.[26] Of paramount importance to the conduct and interpretation of this study is that all patients underwent a standardized surgical operation and all surgical specimens were analyzed using a standardized histopathologic protocol with strict attention to this margin. Specifically, the uncinate process of the pancreas was meticulously dissected from the retroperitoneum directly along the periadventitial plane of the SMA from the first jejunal branch of the SMV to the takeoff of the SMA from the aorta. This dissection removes all the fatty tissue to the right of the SMA that contains blood and lymphatic vessels associated with the pancreatic head and uncinate process—an embryologically defined anatomic region recently described as the "mesopancreas".[16, 31] Following resection, the resulting SMA margin was inked and processed by faculty gastrointestinal pathologists, with serial sections taken perpendicular to the inked margin, within which the shortest distance from cancer cells to the inked margin was measured. Due to the consistency of these surgical and pathologic methods, the SMA margin distance reported herein represents a standard measure of the distance between the primary cancer and the SMA in each patient.

Although the significance of these technical details may seem obvious, they are often neglected. Indeed, in a recent

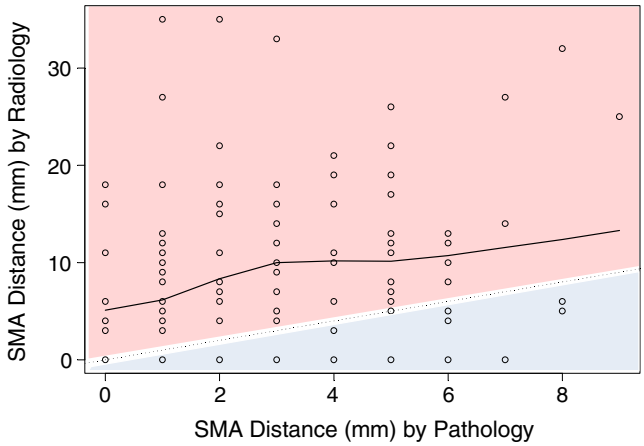

Fig. 4 Scatter plot of superior mesenteric artery (*SMA*) margin distance measured by pathology and estimated by preoperative computed tomography. The *dotted line* corresponds to perfect agreement between the two measures; the SMA margin distances represented at points in *red* were overestimated by radiology and those represented by points in *blue* were underestimated by radiology. The estimated concordance correlation coefficient is 0.07, suggesting poor agreement

analysis of surgical and pathologic standards employed in the treatment of patients with localized PDAC enrolled in a national trial of adjuvant chemoradiation at high-volume pancreatic cancer treatment centers, we found that appropriate dissection of the SMA during surgery was documented in only 25% of cases and histopathologic evaluation of the SMA margin—by any method—was reported in only 47%.[10]

Within this context, we have made several noteworthy observations. First, although our use of meticulous surgical technique with regard to the SMA margin and the delivery of preoperative chemoradiation to the majority of patients led to an extraordinarily low (4%) incidence of a microscopically positive SMA margin, we found that the distance from the primary cancer to the SMA measured <1 mm in an additional 22% of patients. In this and prior studies, we could not demonstrate an independent association between a microscopically positive SMA margin and outcome, perhaps due to a confounding effect of the statistically significant association between preoperative chemoradiation and SMA margin status and margin distance as we demonstrated herein (Table 2).[17] However, to the extent that other studies examining patients who underwent resection as primary therapy have demonstrated a survival advantage associated with R_0 resection,[32, 33] the high incidence of a close margin reported here despite meticulous attention to the SMA dissection has critical implications with regard to the technical aspects of surgery. Techniques of retroperitoneal dissection that do not remove all the soft tissue adjacent to the SMA such as use of the surgical stapler[34]—a dissection method employed by as many of 25% of pancreatic surgeons[10]—may unnecessarily leave cancer cells in situ. Our data suggest an obvious way to improve rates of microscopically complete resection.

Despite the use of high-definition, multidetector CT with a dedicated pancreatic protocol, we also found poor correlation between the standardized SMA distance measured histopathologically and the same distance estimated radiographically. Indeed, we found that the SMA margin distance was routinely overestimated on preoperative CT images. Importantly, this was true even among patients who did not receive preoperative chemoradiation—a group with images not subject to radiographic artifact that may be induced by radiation. Although it might be argued that a selective approach to aggressive dissection of the SMA could be employed based on the radiographic relationship between the primary cancer and SMA on preoperative cross-sectional imaging, these data clearly demonstrate that systematic dissection of the SMA along its periadventitial plane should be routine for all patients.

In this study, patients who received neoadjuvant chemoradiation had longer SMA margin distances than those who underwent surgery first. This was true even though the chemoradiation group contained all of the patients with borderline resectable disease, in whom the primary cancer appeared to abut the great visceral arteries (typically the SMA) on CT prior to receipt of therapy. In addition, the median diameter of the primary cancer in the final surgical specimen was smaller in patients who received chemoradiation than in those who did not. We also noted that the distribution of SMA margin distances following surgery was similar between patients who presented with potentially resectable cancer and those who presented with borderline resectable/locally advanced cancers. Together, these findings represent evidence of the ability of preoperative chemoradiation to "sterilize" surgical margins at the periphery of cancers abutting the SMA, where well-oxygenated cancer cells are most subject to the effects of radiation. These observations provide strong evidence for the use of neoadjuvant treatment sequencing strategies that employ chemoradiation in patients with borderline resectable PDAC.

We found that the preoperative administration of chemoradiation and EBL were independently associated with a longer LPFS and PFS. Although SMA margin distance was associated with LPFS and PFS on univariate analysis, it was not associated with either of these outcome metrics after adjustment for the effects of other covariates (including chemoradiation). However, patients who received neoadjuvant chemoradiation and had a SMA margin distance of ≤1 mm had the highest rates of locoregional and distant recurrence. Together, these findings reveal the significant influence that careful patient selection, treatment sequenc-

ing, and meticulous surgical technique may have upon locoregional control—an important clinical problem given the high incidence of locoregional recurrence among patients treated with or without postoperative therapy and its common association with debilitating symptoms, which can be extraordinarily difficult to manage and have a detrimental effect on quality of life.[1, 7, 35]

Importantly, we could not demonstrate a significant effect of either preoperative chemoradiation or surgical technique upon OS, presumably due to the high incidence of distant recurrence observed in patients with PDAC that often leads to death. Only lower EBL was independently associated with longer OS. In this regard, two points are noteworthy. First, the presence of negative lymph nodes—routinely identified as independently associated with longer OS[21]—was not found to be so in this study because of the high correlation between lymph node status and the administration of chemoradiation (Table 1). Second, although patients who received chemoradiation had a higher blood loss than those that underwent surgery first, this is likely related to the higher incidence of more advanced cancers in that group and should not lead to the outright dismissal of multimodality strategies that employ preoperative chemoradiation for this disease.

Finally, it should be noted that our study demonstrates the importance of standardized terminology in the definition of extent of resection (*R*-status). In this and prior studies, we used the descriptor R_1 to indicate the direct extension of cancer cells up to the margin of resection on microscopic examination. We classified patients with a close but negative margin (cancer cells within 1 mm) as having undergone an R_0 resection. This terminology is supported by both the AJCC and College of American Pathologists.[26, 36] However, other groups, particularly in Europe, classify resections with microscopically negative margins but cancer cells within 1 mm of the margin as R_1.[37] The use of different definitions can clearly contribute to variability in reported rates of positive margins across studies.

In summary, notwithstanding the limitations inherent in this partially retrospective study, we demonstrated that both preoperative chemoradiation and meticulous surgical technique increase the distance between cancer cells and the SMA margin. These clinical components are critical to maximizing margin-negative resection and achieving locoregional cancer control among patients with potentially resectable and borderline resectable PDAC. To the extent that novel chemotherapeutic agents can be expected to reduce systemic recurrence in the future, the clinical importance of strategies designed to limit local recurrence for PDAC may become ever more critical.

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Discussant

Dr. Taylor S. Riall (Galveston, TX): I thank the authors for the opportunity to discuss this excellent manuscript and congratulate them on an outstanding presentation. Dr. Katz and colleagues evaluate the effect of neoadjuvant chemoradiation and meticulous, standardized dissection of the SMA margin in achieving locoregional control in patients with potentially resectable or borderline-resectable pancreatic cancers.

You demonstrate that neoadjuvant chemoradiation provides a wider margin between tumor and the superior mesenteric artery. In addition, you show improved progression-free survival and locoregional progression-free survival. However, there is no difference in overall survival between the two groups. My main question or concern is the following: the outcomes of progression-free and overall survival were not evaluated on an intent-to-treat basis. How many patients with potentially resectable or borderline resectable pancreatic cancer received neoadjuvant therapy, experienced disease progression or functional decline and never made it to surgery? In other words, neoadjuvant therapy, in part, is selecting a group of patients with favorable tumor biology. In order to more accurately estimate the effects of neoadjuvant therapy on survival and patterns of recurrence you should include all patients with potentially resectable and locally advanced pancreatic cancer who received (or did not receive) neoadjuvant therapy regardless of whether they were ultimately resected, otherwise it is impossible to compare the effect of neoadjuvant therapy to that of resection plus adjuvant therapy.

In addition, your study includes borderline resectable patients. The use of neoadjuvant therapy is more intuitive in this group and the study might be cleaner if you just included the potentially resectable patients.

Finally, in your manuscript, you refer to a recent autopsy study on patterns of recurrence in patients with pancreatic cancer by Dr. Iacobuzio-Donahue and colleagues. The study finds that pancreatic cancer seems to be represented by to two phenotypes based on Dpc4 status of the tumor. These phenotypes differ, not in their morphologic appearance at diagnosis, but in their metastatic efficiencies, with tumors that are dpc4 positive (or have not lost dpc4 tumor suppressor expression) being much less likely to metastasize. Do you routinely test the Dpc4 status of tumor on your preoperative biopsies or after resection? If so, do you know how many tumors were Dpc4 positive in each group? Do you think that knowing the Dpc4 status would have implications on therapy? For example, perhaps neoadjuvant chemoradiation most greatly benefits patients with Dpc4 tumors, where local control is an issue?

Thank you for the opportunity to discuss this paper.

Closing Discussant

Dr. Matthew H. G. Katz: We thank the Society for the opportunity to present our work, and Dr. Riall for her excellent questions.

The specific goal of this analysis was to demonstrate the associations, if any, between meticulous surgical technique, preoperative chemoradiation, and long-term oncologic outcome measures among patients who underwent surgical resection. As Dr. Riall appropriately states, we evaluated only patients who completed all therapy including surgery and did not include patients who received neoadjuvant therapy but did not ultimately undergo resection. In past clinical trials of neoadjuvant chemoradiation conducted at our institution, 11% to 46% of patients treated on protocol failed to undergo surgery. Surgical margins and recurrence rates are clearly not applicable to such patients, and therefore we could not evaluate them using the endpoints in this study. We continue to believe, however, that the administration of chemoradiation in the preoperative setting is associated with several important clinical benefits beyond those evaluated as endpoints in this analysis. Specifically, neoadjuvant treatment sequencing assures that all patients who undergo surgery receive all components of multimodality care, targets the microscopic cancer believed to exist in most patients with this disease, and provides a time interval within which to evaluate tumor biology and select patients for whom surgery may be most appropriate. Furthermore, to the extent that we also found a significant association between surgical technique and the distance between cancer and the superior mesenteric artery margin in this study, and given prior data that suggests a survival benefit associated with a microscopically margin-negative resection, our findings suggest an important opportunity for quality improvement regardless of the sequencing strategy employed.

In this analysis, we included patients with both potentially resectable and borderline resectable primary cancers. We chose to evaluate both populations given the accumulating interest in the use of neoadjuvant chemoradiation for patients with each of these disease stages. For patients with borderline resectable cancers, in whom tumor abutment of the visceral arteries may otherwise lead to palliative (not curative) care, the administration of neoadjuvant chemoradiation may be particularly critical. Indeed, the recent AHPBA/SSO consensus statement advocates the administration of preoperative chemoradiation to these patients. Unfortunately, little data exist to specifically support this recommendation. This absence of data is particularly notable given the recent enthusiasm for FOLFIRINOX, the efficacy of which may lead some to question the necessity of radiation for patients with borderline cancers. Our data suggest that preoperative chemoradiation has cytotoxic effects particularly at the interface between the cancer and superior mesenteric artery, and provide important support for the use of preoperative chemoradiation in patients with borderline resectable tumors.

One of the reasons we have found neoadjuvant treatment sequencing so appealing is that its use facilitates the development of personalized therapeutic strategies that can be individualized to each patient's physiology, tumor biology and tumor anatomy. In this regard, we would welcome any novel diagnostic test that would assist in therapeutic decision making. Although historically we have not routinely tested the DPC-4 status of each patient prior to or following resection, we are actively investigating its potential role in the care of patients with localized pancreatic cancer.