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Radiographic Tumor-Vein Interface as a Predictor of Intraoperative, Pathologic and Oncologic Outcomes in Resectable and Borderline Resectable Pancreatic Cancer

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Abstract

Background—Venous resection may be required to achieve complete resection of pancreatic cancers. We assessed the ability of radiographic criteria to predict the need for superior mesenteric-portal vein (SMV-PV) resection and the presence of histologic vein invasion.

Methods—All patients who underwent pancreaticoduodenectomy from 2004-2011 at the authors' institution were identified. Preoperative pancreatic protocol CT images were re-reviewed to characterize the extent of tumor-vein circumferential interface (TVI) as demonstrating no interface, 180 degrees of vessel circumference, > 180 degrees of vessel circumference, or occlusion. Findings were correlated with the need for venous resection, histologic venous invasion and survival.

Results—254 patients underwent pancreaticoduodenectomy and met inclusion criteria; 98 (39.6%) required SMV-PV resection. In our cohort, 76.4% of patients received neoadjuvant chemoradiation. The TVI classification system predicted with fair accuracy both the need for

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SMV-PV resection at the time of surgery and histologic invasion of the vein. In particular, 89.5% of patients with TVI > 180 degrees or occlusion required SMV-PV resection. Of those, 82.4% had documented histologic SMV-PV invasion. TVI > 180 degrees was associated with favorable overall survival compared to a greater circumferential interface.

Conclusions—A tomographic classification of the tumor-SMV-PV interface can predict the need for venous resection, pathologic venous involvement and survival. To assist in treatment planning, a standardized assessment of this anatomic relationship should be routinely performed.

Keywords

pancreatic adenocarcinoma; borderline resectable; superior mesenteric vein; portal vein; computed tomography

INTRODUCTION

Tumor invasion of the superior mesenteric vein/portal vein (SMV-PV) by pancreatic ductal adenocarcinoma of the head of the pancreas (PDAC) is common due to the anatomic proximity of the venous confluence to the pancreatic head. Historically, such vascular involvement represented a contraindication to surgical resection because it was perceived that pancreaticoduodenectomy (PD) with concomitant vein resection—often performed by an unprepared surgical team following intraoperative identification of venous involvement by cancer—was a high-risk operation associated with a low likelihood of yielding a complete resection of the tumor and long-term survival [1,2]. Over the past two decades, however, improvements in cross-sectional imaging have allowed for more detailed preoperative planning and have contributed to operative safety. In addition, improvements in neoadjuvant therapies have resulted in a larger group of patients being considered for extended surgical procedures involving the SMV-PV. Multiple recent series have demonstrated that venous resection and reconstruction during pancreaticoduodenectomy (PD) can now be performed safely and may result in favorable survival rates in properly selected patients [3-5]. Many pancreatic treatment centers now routinely perform venous resection and reconstruction with PD, with or without neoadjuvant therapy.

Characterization of the anatomic relationship between tumor and vessels on radiographic images has thus become a critical step in the preoperative and intraoperative decision-making processes for patients with PDAC. Several radiographic classification systems have been developed to describe this relationship in an effort to alert the operative team for the potential need for vascular resection/reconstruction [6-9]. However, few studies have explored the association between radiographic indicators and either histopathologic findings or long-term oncologic outcomes. Furthermore, the radiographic classification systems that have been developed have assumed a surgery first treatment algorithm. Their applicability following treatment with preoperative therapy—increasingly used in the management of patients with both resectable and borderline resectable tumors that involve the mesenteric vasculature—is therefore unknown.

In this study, we sought to evaluate the ability of a simple set of tomographic criteria to predict the need for venous resection at the time of surgery, the presence of histologic

invasion of the vein wall, and the overall survival of patients who had and had not received chemoradiation therapy prior to PD. To this end, we re-reviewed the preoperative cross-sectional imaging studies of 277 consecutive patients who underwent curative resection of pancreatic head adenocarcinoma and correlated the circumferential radiographic interface between the primary tumor and SMV-PV with intraoperative events, histopathologic results and long-term oncologic outcomes.

PATIENTS AND METHODS

The institutional review board of the University of Texas M.D. Anderson Cancer Center approved this study. Clinical data on all patients who underwent PD for PDAC between 2004 and 2011 at MDACC were retrieved from the institutional pancreatic tumor database prospectively maintained by the Department of Surgical Oncology [10]. Patients who did not receive preoperative computed tomography (CT) imaging using pancreatic protocol within three months of surgery were excluded from analysis, as were patients whose final diagnosis was invasive PDAC arising from an intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN).

Radiographic Evaluation

Anatomic disease evaluation was accomplished with multi-detector CT using a 16-detector or 64-detector row scanner (General Electric Medical Systems, Milwaukee, WI) and a standard protocol optimized for imaging pancreatic tumors, which consisted of a multiphasic CT with pre-contrast, late arterial, and portal venous phases of enhancement. The pre-contrast study extended from the top of the liver to the bottom of the liver. The late arterial phase of enhancement was typically obtained between 25 to 40 seconds from the start of the injection and the portal venous phase at 60 to 70 seconds delay. These phases covered the dome of the liver to the iliac crest. Delayed imaging through the kidneys at 90 seconds was also performed. Iodinated contrast was injected intravenously at a rate of 4 to 5 cc/second via a power injector. The portal venous phase of enhancement was used for evaluation of the portal, portal venous confluence and the superior mesenteric veins.

The preoperative CT images of each eligible patient were re-reviewed for this study by a gastrointestinal radiologist faculty (A.B.), who was blinded to each patient's clinical history. The circumferential interface between the primary tumor and SMV-PV was measured on axial images and designated as: none (no direct interface, with either normal pancreas or fat separating the primary tumor from the vessel), 180 degrees of the vessel circumference, > 180 degrees of the vessel circumference, or vascular occlusion (i.e., an absence of contrast within the lumen of the vein in association with adjacent tumor) (Figure 1). Although we routinely apply these tumor-vessel interface descriptors to both arteries (superior mesenteric artery, common hepatic artery, celiac trunk) and veins (SMV-PV) for radiographic staging purposes, here we sought to evaluate the ability of a simple set of radiographic criteria to predict both the need for superior mesenteric vein-portal vein (SMV-PV) resection at pancreatectomy and the histologic presence of SMV-PV invasion, so we focused on the tumor-vein interface (TVI) only [11,12].

Neoadjuvant Chemoradiation

When administered, neoadjuvant chemoradiation consisted of external beam radiation therapy to either 30 Gy in 10 fractions or 50.4 Gy in 28 fractions with concurrent capecitabine, fluorouracil or gemcitabine using a three-dimensional conformal technique. Gemcitabine-based systemic chemotherapy was delivered prior to chemoradiation in selected cases.

Surgical and Histopathologic Techniques

PD was performed using a standard technique [13]. The decision to perform venous resection and reconstruction was made by the operating surgeon based on an intraoperative assessment of the relationship between tumor and vein. When the primary tumor was adherent to and not easily separable from the vein, SMV-PV resection was performed either tangentially or segmentally as previously described [14]. Reconstruction of tangential resection consisted of either primary vein closure or patch venoplasty; segmental resection required bypass graft reconstruction with autologous internal jugular vein or rarely, bioprosthetic material [15].

Pathologic evaluation of the specimen was performed using a standardized system and surgical margins were designated in accordance with criteria of the 7th edition of the American Joint Committee on Cancer Staging Manual [16]. The final margin status of PD specimens was recorded as R0 (all margins negative microscopically), R1 (all margins grossly negative, but tumor cells present at any of the resected margins microscopically), or R2 (tumor identified grossly and microscopically at any of the margins). The closest distance between cancer cells and the superior mesenteric artery (SMA) margin was measured microscopically and prospectively recorded [13].

When applicable, the resected portion or segment of the SMV-PV was entirely submitted for histologic assessment. The inked vein margins were evaluated either perpendicularly for tangential SMV-PV resections or en face for segmental SMV-PV resections. Vein involvement by tumor was divided microscopically into 4 groups: 1) no tumor involvement; 2) tumor invasion into the tunica adventitia; 3) tumor invasion into the tunica media or intima; and 4) tumor invasion into the lumen of the SMV-PV with or without associated thrombus (Figure 2) as previously described [15]. For clinicopathologic correlations, all patients who had SMV-PV resection but no histologic tumor involvement of the resected vessel and those who did not undergo SMV-PV resection at the time of PD (because the tumor was easily separable from the vein) were considered to have no vein involvement. Patients with proven histologic tumor invasion into any layer of the vein wall or its lumen were considered to have vein involvement by histology.

Follow-up and Statistical Analysis

Summary statistics were used to describe the study population. T-test (or one way ANOVA) and Pearson chi-square test (or Fisher's exact test) were used to assess differences in clinical/demographic characteristics by TVI categories, by venous resection, and by final pathologic results. Receiver operating characteristics (ROC) curves were constructed and the areas under the curve (AUC) were calculated to evaluate the ability of TVI classification to

predict intraoperative need for vein resection and presence of vein invasion. Overall survival (OS) was defined as the time from diagnosis to death or to the date of last follow-up if death did not occur. Progression-free survival (PFS) was calculated as the time from diagnosis to recurrence or death. The Kaplan-Meier product limit method was used to estimate the median survival durations for each clinical/demographic factor. Univariate Cox proportional hazard regression was used to identify any association between each of the variables and survival duration. Similar analyses were performed for PFS. Factors with a p-value ≤ 0.10 were included in the multivariate analyses. Statistical analysis was performed using Stata/SE version 12.1 statistical software (Stata Corp. LP, College Station, TX).

RESULTS

Clinicopathologic patient profile

277 patients with PDAC of the pancreatic head meeting inclusion criteria for this retrospective review underwent pancreaticoduodenectomy at MDACC from 2004 to 2011. The standardized institutional preoperative imaging study was not performed prior to surgery in 11 patients who were therefore excluded from the study, as were 12 additional patients whose final pathology demonstrated PDAC arising from a mucinous precursor lesion. The clinicopathologic characteristics of the remaining 254 patients are reported in Table 1. Radiologic re-review of preoperative imaging studies classified the TVI of these patients as: no interface (n = 62, 24.4%), ≤ 180 degrees (n = 154, 60.6%), > 180 degrees (n = 28, 11.0%) and occlusion (n = 10, 3.9%).

Chemoradiation with or without induction chemotherapy was administered to 194 (76.4%) patients prior to resection. At surgery, SMV-PV resection and reconstruction was performed in 98 (38.6%) of 254 patients (58 via segmental resection and 40 via tangential resection), of whom 10 underwent concomitant resection of the common hepatic artery and/or its primary branches. Of the 98 patients who underwent SMV-PV resection and reconstruction, the initial histopathologic examination of the resected vein of 5 patients was incomplete and insufficient material existed for re-review. Among the remaining 93 patients with a complete histopathologic assessment of the vein, the wall of the resected vein was invaded by cancer in 64 (68.8%): 17 tumors involved the tunica adventitia, 42 the tunica media/intima, and 5 invaded into the vein lumen.

TVI as a Predictor of Surgical and Pathologic Outcomes

Clinical characteristics and outcomes for each TVI category are reported in Table 2. Primary cancers with a greater circumferential TVI were larger, more likely to have been treated with neoadjuvant CRT, and more likely to have required SMV-PV resection at pancreatectomy ($p < 0.001$). SMV-PV resection was performed in 8 (12.9%) of the 62 patients with no TVI, 56 (36.4%) of the 154 patients with a TVI ≤ 180 degrees, 25 (89.3%) of the 28 patients with a TVI > 180 degrees, and 9 (90.0%) of the 10 patients with venous occlusion ($p < 0.001$). The rate of microscopically negative margins (R0 resection) among patients treated surgically was similar across TVI groups ($p = 0.25$).

Receiver operating characteristics (ROC) curves were constructed to evaluate the ability of preoperative TVI to predict the need for SMV-PV resection and reconstruction (Figure 3A). A TVI threshold of any interface was associated with a high sensitivity (91.8%) and negative predictive value (NPV, 87.1%) for SMV-PV resection, but a low specificity (34.6%). Increasing the TVI threshold to 180 degrees was associated with high specificity (97.4%) and positive predictive value (PPV, 89.5%) for SMV-PV resection, but a low sensitivity (34.7%). The area under the ROC curve (AUC) was 0.734 (Figure 3A).

Histopathologic vein involvement was identified in 2 (3.2%) patients with no preoperative TVI (28.6% of patients with no TVI who underwent SMV-PV resection); 34 (22.7%) patients with TVI $\leq$ 180 degrees (65.4% of patients with TVI $\leq$ 180 degrees who underwent SMV-PV resection); 20 (71.4%) patients with TVI $>$ 180 degrees (80.0% of patients with TVI $>$ 180 degrees who underwent SMV-PV resection) and 8 (80.0%) patients with venous occlusion (88.9% of patients with venous occlusion who underwent SMV-PV resection). The AUC of the ROC curve constructed to evaluate the ability of preoperative TVI to predict SMV-PV invasion was 0.768 (Figure 3B).

Subgroup analyses of patients resected with and without prior administration of chemoradiation therapy are reported in Table 2.

Follow-Up and Survival

At the time of last follow-up, 159 (62.6%) of the 254 patients had died. The median follow-up from the date of diagnosis of the 95 patients still alive was 47.1 months. For the 254 study patients, median PFS was 17.7 months (95% confidence interval [CI], 15.6 – 20.2) and median OS was 33.1 months (95% CI, 29.8 – 40.4).

Resection and reconstruction of the SMV-PV at the time of pancreatectomy was associated with shorter median PFS (16.1 vs. 19.6 months, $p = 0.013$) and OS (27.8 vs. 44.5 months, $p = 0.002$) than pancreatectomy alone. Similarly, patients with vein involvement confirmed by histology had a shorter median PFS (15.6 vs. 19.6 months, $p = 0.001$) and OS (27.0 vs. 40.4 months, $p = 0.001$) than patients without tumor involvement of the vein. For survival analyses, patients were grouped into two main TVI groups: those with either no interface or a TVI measuring $\leq$ 180 degrees, and those with a TVI measuring $>$ 180 degrees. This decision was based on the fact that the survival curve of patients with no interface was similar to that of patients with a TVI measuring $\leq$ 180 degrees, and that the survival curve of patients with a TVI measuring $>$ 180 degrees was similar to that of patients with venous occlusion. Patients with TVI $\leq$ 180 had a shorter median PFS (15.9 vs. 18.2 months, $p = 0.006$) and OS (30.9 vs. 37.3 months, $p = 0.030$) than patients with an interface $\leq$ 180 degrees (Figure 4).

DISCUSSION

Here we evaluated objective radiographic, clinical and pathologic parameters to determine the ability of the circumferential interface between the primary tumor and SMV-PV on preoperative CT images to predict the need for venous resection at PD, histopathologic invasion of the vein wall in the surgical specimen, and overall survival of patients with

PDAC. Among 254 patients who underwent surgical resection as either primary therapy or following neoadjuvant chemoradiation, both vein resection at PD and histopathologic involvement of the vein were more common among patients with a greater TVI on preoperative images. Although microscopically negative margins were achieved in over 90% of patients regardless of the extent of preoperative TVI, an interface > 180 degrees was associated with shorter PFS and OS following resection. TVI thus represents a relevant clinical parameter that should be routinely measured and documented in standardized radiographic reports.

It has been well established that cross-sectional imaging studies of the pancreas provide information useful for perioperative planning. Prior studies have characterized the local anatomy on the basis of the radiographic relationship between tumor and vessel [6,7,9,14] or the radiographic appearance of the vessel itself [8] and have used classification schemes ranging from the simple [7,14] to relatively complex [6,8,9] on the basis of either cross-sectional CT images [6,7,9,14] or mesenteric angiograms [8]. Here, we have categorized TVI using a simple, objective scheme that characterizes the radiographic interface between primary tumor and SMV-PV as observed on routine cross-sectional CT images. Importantly, in describing this relationship, we have refrained from using subjective radiographic terms that have historically contributed to confusion with regard to local disease staging. For example, current NCCN guidelines distinguish resectable from borderline resectable cancers on the basis of “venous *involvement* of the SMV-PV demonstrating tumor *abutment* with *impingement* and *narrowing* of the lumen, *encasement* of the SMV-PV but without encasement of the nearby arteries, or short-segment venous occlusion” [17]. This terminology used in these guidelines leaves significant ambiguity as to which tumors should be considered resectable and which should be considered borderline resectable. To the extent that stage-specific treatment algorithms are dependent upon such designations [18], the objective schema reported here may be used to individualize and optimize the treatments administered to patients with localized PDAC.

Because resection of the adjacent mesenteric vasculature was historically viewed as the primary local contraindication to pancreatectomy, early studies primarily assessed the ability of radiographic observations to predict intraoperative inseparability of the tumor from the adjacent vessels [7,9,14]. As vascular resection has become increasingly accepted, additional work has examined the relationships between radiographic and histopathologic findings and prognosis following vein resection [8,14,19,20]. One study worthy of highlight is from Nakao et al., which reported a single-institution series of 358 patients who underwent *de novo* pancreatectomy over a period of 19 years [19]. On the basis of the appearance of the SMV-PV (type A [normal], type B [unilateral narrowing of the vein], type C [bilateral narrowing], or type D [stenosis or obstruction with collaterals]), the authors reported rates of PV resection of 19% of patients with type A, 94% with type B, 99% with type C, and 100% with type D radiographic anatomy, and corresponding rates of pathologic PV wall invasion of 0%, 51%, 74%, and 93%, respectively.

Despite their low threshold for vein resection, the authors achieved R0 rates of 80% for type A, 73% for type B, 57% for type C, and 40% for type D tumors. Survival of patients with type C/D anatomy was shorter than that of patients with type A/B anatomy.

We likewise found that PDAC of the pancreatic head that extend to the left of the SMV-PV have a more aggressive biologic phenotype than tumors that do not, regardless of the use of vein resection; in our series, patients with a TVI > 180 degrees had a shorter median PFS and OS than patients with no interface or a more limited interface. Importantly, however, the R0 resection rate was higher in our series—over 90% in each TVI group—and did not differ based on the circumferential extent of TVI. The difference between our results and those from Nakao et al. may be due to our bias toward the administration of neoadjuvant chemoradiation (often in addition to systemic therapy) to all patients with borderline resectable PDAC, a practice not employed by Nakao even for more locally invasive cancers. Whether the high rate of margin-negative resection reported here despite extensive venous involvement is a reflection of the purported “sterilizing” effects of radiotherapy on surgical margins or selection bias, which is an important effect of neoadjuvant treatment sequencing, is unclear. Nevertheless, to the extent that most patients with PDAC die with local disease [21] and that future improvements in systemic therapies are likely to further emphasize the role for local cancer control, our findings suggest that chemoradiation may be a particularly important component of therapy for patients with radiographic evidence for significant venous involvement.

As a predictive tool, TVI criteria achieved fair accuracy in predicting the need for venous resection and histopathologic vein invasion. Absence of TVI on preoperative imaging was still associated with SMV-PV resection in 8 of 62 cases, but the vein was histologically involved by tumor in only 2 of them. On the other hand, a TVI > 180 degrees or venous occlusion was highly associated with both the need for venous resection and with histologic vein invasion. As expected, the least predictable TVI category was when the tumor shared an interface with up to half the circumference of the SMV-PV. In patients with such findings, vein resection was performed in over 1/3 of the patients, with 65% of resected veins having histologic evidence of vein invasion. It is important to note that equivocal radiographic categories for determining vascular involvement or tumor resectability are not a function of this specific set of CT criteria, but instead represent a category of tumor-vessel relationship that exists across classification systems and commonly features some degree of unilateral vessel involvement, such as grade 2 of the Raptopoulos system (flattening or slight irregularity on one side of the vessel) [6], grade 2 of the Lu criteria (tumor is contiguous with 25-50% of the vessel circumference) [7,22], or types II and III of the Ishikawa system (tumor causes a smooth shift and unilateral narrowing, respectively, of the PV) [8,23]. Together, these findings suggest that 1) veins that bear no direct interface with the tumor are highly unlikely to require resection, and even less so to harbor malignancy if resected; 2) conversely, SMV-PVs with more than 180 degrees of tumor interface or occlusion by the tumor are highly likely to need resection and to harbor malignancy; and 3) SMV-PVs that share an interface < 180 degrees with the tumor may need to be resected and may harbor malignancy. This last point underscores the fact that, although preoperative imaging can be a useful adjunct in anticipating the need for SMV-PV resection, ultimately this decision rests with the operating surgeon at the time of surgery, who may deem this step necessary to safely resect the tumor and/or achieve clear surgical margins. Continued attempts at separating the pancreas tumor from the SMV-PV that result in either an inadvertent venotomy or a grossly positive margin of resection must be avoided. A carefully

planned venous resection/reconstruction is a much safer and oncologically superior operation.

Despite the significant number of patients in this series who had relatively advanced disease, the median OS for our entire study population, 33.1 months, compares favorably to published survival statistics for patients with resected PDAC [5,24,25]. Multiple studies have shown that SMV-PV resection and reconstruction can be performed safely as part of PD in well-selected patients, but conflicting data exist with regard to the association between vein resection and OS [3-5, 26]. In this series of patients treated 2004 to 2011, patients who did not undergo vein resection concomitant with PD had a significantly longer OS (median 44.5 v. 27.8 months, $p = 0.002$) than that of patients who did. In our previous report of patients who underwent pancreaticoduodenectomy at our institution between 1990 and 2002, the median OS of patients who underwent venous resection (23.4 months) was similar to that of patients who did not (26.5 months, $p = 0.18$) [3]. The difference in these two studies, which largely reflects a relative improvement in survival among patients who did not require vascular resection (rather than a deterioration in survival among those who did), is likely due to improved patient selection (for example, the detection of small liver metastases on CT which were not visible in the past), increased experience of the multidisciplinary treatment team and all hospital providers, and more effective systemic therapies.

It is important to emphasize that we included only patients who underwent pancreatectomy in this study, and reviewed only the preoperative CT scan. We did not examine changes in TVI that may have occurred in response to neoadjuvant therapy. In a recent analysis of patients with borderline resectable PDAC, many of whom are also reported in the present study, we demonstrated that significant radiographic “downstaging” was observed in the CT scans of only 1 of 129 patients [27]. The current report also excluded patients whose pancreatectomy was aborted based on intraoperative findings. At our institution, however, this is a rare event; among 92 patients in the previously cited study who were brought to the operating room for planned pancreatectomy, only 3 patients did not undergo resection due to unsuspected locally advanced disease [27]. These potential limitations notwithstanding, this study is notable for several fundamental strengths. First, our findings reflect the broad experience of a quaternary center for pancreatic disease that evaluates a significant number of “borderline resectable” cancers. Indeed, 76% of the patients reported in this study, all of whom underwent pancreatectomy, had a direct radiographic interface between tumor and the SMV-PV prior to surgery, and in 20% of such patients this interface measured >180 degrees or was associated with complete venous occlusion. Our center therefore performs vascular resection in nearly 40% of all pancreatic cancer operations. All patients were evaluated using a standardized, high-quality imaging protocol optimized for pancreatic imaging. We used standardized indications for surgery, standard operative techniques, and uniform methods of histopathologic analysis of the surgical specimen to include histologic review of the resected SMV-PV. Finally, all imaging studies were re-reviewed for this analysis by a single gastrointestinal radiologist faculty to achieve uniform interpretation of the pre-operative CT images in our study population.

CONCLUSION

In summary, a simple radiographic classification system that categorizes the circumferential interface between the tumor and the SMV-PV on preoperative imaging can be used to predict the need for SMV-PV resection at the time of pancreatectomy, histopathologic invasion of the resected vein, and overall prognosis of patients with resectable and borderline resectable PDAC. A standardized description of this anatomic relationship should be a routine part of all CT reports in patients with localized PDAC, may influence treatment sequencing decisions, and may assist in the referral of patients to centers experienced with vascular resection/reconstruction at the time of pancreatectomy for cancer.

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Figure 1. Radiographic classes of tumor vein interface

A. The tumor (T) shares no direct interface with the SMV-PV (*). **B.** The tumor (T) shares an interface measuring 180° of the SMV-PV (*) circumference (arrow). **C.** The tumor (T) shares an interface measuring $> 180^\circ$ of the SMV-PV (*) circumference (arrows). **D.** The tumor (T) is associated with occlusion of the SMV-PV (*) (arrow), which occurs just distal to this image.

Figure 2. Histopathologic evaluation of the resected SMV-PV

Representative micrographs show a resected SMV-PV wall that is free of carcinoma (A), and tumor invasion (arrows) into the wall (media) of the SMV-PV (B). Hematoxylin & eosin (H & E) stain; original magnification: 100 $\times$.

Figure 3. Receiver operating characteristics (ROC) curves evaluating the TVI classification system as a predictor of SMV-PV resection (A) and histologic SMV-PV involvement by tumor (B)

The areas under the curve (AUC) were 0.734 for SMV-PV resection and 0.773 for SMV-PV histologic involvement.

Figure 4. Cumulative Progression-Free Survival (PFS) and Overall Survival (OS) rates according to degree of Tumor-Vein Interface (TVI)

Patients whose TVI measured up to 180° of the SMV/PV circumference experienced longer PFS (A) and OS (B) than those with a TVI measuring > 180° of the vein circumference.

Table 1

Clinicopathologic characteristics of study population stratified by receipt of neoadjuvant chemoradiation.

Characteristics	All patients (n = 254)	Neoadjuvant CRT (n = 194)	No neoadjuvant CRT (n = 60)	P-value
Age at diagnosis, mean $\pm$ SD	63.6 $\pm$ 9.5	64 $\pm$ 9.4	63 $\pm$ 10.0	0.80
Female gender	121 (47.6%)	90 (46.4%)	31 (51.7%)	0.48
TVI category				< 0.001
No interface	62 (24.4%)	35 (18.0%)	27 (45.0%)	
180°	154 (60.6%)	122 (62.9%)	32 (53.3%)	
> 180°	28 (11.0%)	27 (13.9%)	1 (1.7%)	
Occlusion	10 (3.9%)	10 (5.2%)	0 (0.0%)	
SMV-PV resection	98 (38.6%)	86 (44.3%)	12 (20.0%)	0.001
Histologic vein invasion, n (%) ^a	64 (25.7%)	57 (30.0%)	7 (11.9%)	0.005
Tumor size (cm), mean $\pm$ SD	2.0 $\pm$ 1.4	2.0 $\pm$ 1.5	2.3 $\pm$ 1.1	0.13
R0 resection status	238 (93.7%)	184 (94.8%)	54 (90.0%)	0.18
NI, n (%)	149 (58.7%)	98 (50.5%)	51 (85.0%)	< 0.001

Abbreviations: CRT, chemoradiation; TVI, tumor-vein interface; SMV-PV, superior mesenteric vein-portal vein

^a Five patients with missing histologic information on the resected vein (4 in neoadjuvant CRT subset, 1 in surgery first subset) were excluded from the denominator

Table 2

Clinicopathologic features by TVI categories.

Characteristics	TVI Category				P-value
	None	180 degrees	> 180 degrees	Occlusion	
<i>All Patients</i>					
Patients, N	62	154	28	10	
SMV-PV resection, n (%)	8 (12.9%)	56 (36.4%)	25 (89.3%)	9 (90.0%)	< 0.001
Histologic vein invasion, n (%)	2 (3.3%) ^a	34 (22.7%) ^b	20 (71.4%)	8 (80.0%)	< 0.001
Tumor size (cm) ± SD	1.6± 1.6	2.0± 1.4	2.5± 1.3	3.4± 1.3	< 0.001
R0, n (%)	61 (98.4%)	141 (91.6%)	26 (92.9%)	10 (100.0%)	0.25
N1, n (%)	43 (69.4%)	86 (55.8%)	15 (53.6%)	5 (50.0%)	0.25
<i>Neoadjuvant CXRT</i>					
Patients, n	35	122	27	10	--
SMV-PV resection, n (%)	5 (14.3%)	48 (39.3%)	24 (88.9%)	9 (90.0%)	< 0.001
Histologic vein invasion, n (%)	1 (2.9%) ^a	29 (24.4%) ^b	19 (70.4%)	8 (80.0%)	< 0.001
Tumor size (cm), mean ± SD	1.4± 1.5	1.9± 1.4	2.5± 1.4	3.4± 1.3	< 0.001
R0, n (%)	35 (100.0%)	114 (93.4%)	25 (92.6%)	10 (100.0%)	0.39
N1, n (%)	19 (54.3%)	60 (49.2%)	14 (51.9%)	5 (50.0%)	0.97
<i>Surgery First</i>					
Patients, n	27	32	1	0	--
SMV-PV resection, n (%)	3 (11.1%)	8 (25.0%)	1 (100.0%)	N/A	0.079
Histologic vein invasion, n (%)	1 (3.7%)	5 (16.1%) ^b	1 (100.0%)	N/A	0.034
Tumor size, (cm), mean ± SD	2.0 ± 1.0	2.5± 1.1	3.0	N/A	0.055 ^c
R0, n (%)	26 (96.3%)	27 (84.4%)	1 (100.0%)	N/A	0.28
N1, n (%)	24 (88.9%)	26 (81.3%)	1 (100.0%)	N/A	0.57

Abbreviations: TVI, tumor-vein interface; CRT, chemoradiation; SMV-PV, superior mesenteric vein-portal vein

^aOne patient who had missing histologic result of the resected SMV-PV was excluded from the denominator (neoadjuvant CRT subset)

^bFour patients (3 in neoadjuvant CRT subset, 1 in surgery-first subset) who had missing histologic results of the resected SMV-PV were excluded from the denominator

^cComparison between first two TVI categories only because there was only one patient in the > 180 degrees group and none in the occlusion group