Resection of Portovenous Structures to Obtain Microscopically Negative Margins during Pancreaticoduodenectomy for Pancreatic Adenocarcinoma Is Worthwhile

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Locally advanced pancreatic adenocarcinoma may require resections of the portal vein and/or its major tributaries to achieve tumor extirpation, albeit with the potential for increased morbidity and mortality. However, major venous resections can impart complete tumor extirpation and thereby a survival advantage compared with resections with residual microscopic disease. This study was undertaken to determine if resection of the portal vein and/or its splenic or superior mesenteric venous (SMV) tributaries is a worthwhile endeavor. Since 1995, patients undergoing pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma have been prospectively followed. The impact of portovenous resections (portal vein, SMV, and/or splenic vein) on survival was evaluated using survival curve analysis (Mantel-Cox test). Margins were codified as R0 or R1 and data are presented as median, mean ± SD where appropriate. For 220 patients undergoing PD for pancreatic adenocarcinoma, survival was 17 months. Patients undergoing R0 resections had improved survival relative to patients undergoing R1 resections (20 *vs* 13 months, $P < 0.03$). Concomitant portovenous resections were undertaken in 48 patients. There was no difference in survival after PD without portovenous resection (17 months) *versus* PD with portovenous resection (18 months). Resections with complete tumor extirpation (i.e., R0 resections) provide superior long-term survival; all efforts to obtain R0 resections should be undertaken. Portovenous resections during pancreaticoduodenectomy can be undertaken safely and are worthwhile when complete tumor extirpation is attainable.

PANCREATIC CANCER IS the fourth leading cause of cancer death in the United States.[1] Two of three patients with pancreatic cancer present with locally advanced unresectable tumors or metastatic disease that precludes operative intervention for all but palliative purposes. Patients undergoing complete tumor extirpation have been shown to have significantly improved survival relative to patients with residual microscopic or macroscopic disease.[2] The 5-year survival rates for patients undergoing R0 resections are as high as to 20 per cent.[3] However, when compared with R0 resections, patients who have tumors resected with positive margins have inferior survival after pancreaticoduodenectomy.[4–6]

There are no universally accepted criteria for resection; each patient should be evaluated on an individual basis. Recent data from M.D. Anderson Cancer Center has defined "borderline resectable" tumors as severely impinging the superior mesenteric vein (SMV) or portal vein or short-segment occlusion of the SMV with vessel patency proximally and distally.[3] Patients with short-segment occlusion and lesser involvement of the portal vein or its major tributaries by tumor invasion should therefore be given full consideration for resection despite the inherent difficulties of such a resection and an increased likelihood for an incomplete resection. Because of the likelihood of incomplete cancer extirpation in the setting of major venous involvement, controversy exists whether involvement of portovenous structures precludes meaningful survival secondary to aggressive tumor biology and thereby should prohibit resection.[7] Furthermore,

Presented at the Annual Scientific Meeting and Postgraduate Course Program, Southeastern Surgical Congress, Atlanta, Georgia, February 7–10, 2009.

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portovenous resections carry the increased risk of perioperative complications, which also can negatively impact both disease-free and overall survival.

We undertook this study to determine the efficacy of portovenous resections during pancreaticoduodenectomy for pancreatic adenocarcinoma. We, like others, believe that portovenous resections can be undertaken without notably increased morbidity and mortality.[8–25] Furthermore, we believe that such resections are particularly worthwhile when R0 resections (microscopically/macroscopically negative margins) are possible because such resections lead to improved survival when compared with R1 resections (microscopically positive, macroscopically negative).[4–6] It is our hypothesis that patients requiring portovenous resections to achieve complete tumor extirpation will have equivalent survival when compared with patients undergoing R0 resections without the need for major portovenous vascular resection, effectively converting an otherwise R1 resection to an R0 resection.

Materials and Methods

Data Management

A prospective database involving all patients treated for pancreatic cancer at our institution was begun in 1996. Patients were entered into this database with Institutional Review Board approval after giving informed consent. Data were stored in Microsoft Excel (Microsoft Corp, Redmond, WA) files. Statistical analysis used Graphpad Instat Version 3.06 and Graphpad Prism 5 (Graphpad Software Inc., San Diego, CA). Survival curve analysis was also undertaken on Graphpad Prism 5, which permitted the log rank and Wilcoxon tests on Kaplan-Meier survival curves. Where appropriate, data are presented as median, mean ± standard deviation.

Preoperative Evaluation

Preoperatively, patients underwent staging with CT scanning. Patients underwent endoscopic ultrasonography evaluation when additional characterization of the mass was warranted or a biopsy was needed. Biopsies were not routinely obtained from pancreatic masses. Endoscopic retrograde cholangiopancreatography with stenting was undertaken when biliary decompression before surgical intervention was warranted. Patients with pancreatic masses thought to have potential for complete tumor extirpation with no evidence of distant metastasis were taken to the operating room. A patent portal vein and superior mesenteric vein were necessary, although focal encasement or occlusion did not preclude exploration.

Intraoperative Management

Intraoperative frozen sections of the pancreatic and common bile duct margins were routinely undertaken to confirm negative margins. Frozen section of additional margins were undertaken as needed when there was a high suspicion of invasion. If negative margins were not achieved, subsequent resections and frozen sections were undertaken to achieve negative margins when possible. Portovenous resections were undertaken as indicated in patients who had the potential for complete tumor extirpation. Portovenous resections were generally undertaken en bloc with the tumor; frozen section analysis of the tumor–portal vein/SMV interface was generally not obtained before venous resection. Rather, portovenous structure resections were undertaken based on intraoperative findings.

Results

Pancreaticoduodenectomy for pancreatic adenocarcinoma was undertaken in 220 patients, 49 per cent men and 51 per cent women, with an age of 68, 68 ± 9.6 years, respectively (Table 1). Concomitant resection of the portal vein or its major tributaries was undertaken in 48 patients: resection of the portal vein in 38 patients, resection of the superior mesenteric vein at the confluence in seven patients, resection of the confluence in two patients, and resection of the splenic vein at the confluence in one patient. Reconstruction was undertaken using lateral venorrhaphy in 44 patients, saphenous vein grafts in two patients, and end-to-end anastomoses in two patients.

Overall survival for all patients was 17 months, 24 ± 24.6 months. There was no difference in survival after pancreaticoduodenectomy without portovenous resection (17 months, 24 ± 24 months) *versus* pancreaticoduodenectomy with portovenous resection (18 months, 26 ± 26 months) (Fig. 1). One hundred sixty-five patients underwent R0 resections and 55 patients underwent R1 resections. Patients undergoing R0 resections lived longer; patients undergoing R0 resections had an overall survival of 20 months, 26 ± 23.5 months, whereas patients undergoing R1 resections had an overall survival of 13 months, 20 ± 27.6 months ($P = 0.003$). When patients were stratified by margin status, overall survival was not impacted by the necessity for concomitant portovenous resection (Table 2; Figs. 2 and 3).

Of the 55 patients undergoing R1 resections, 13 (27%) underwent concomitant portovenous resections in an attempt at complete tumor extirpation. There was no significant difference in the rate of R1 resections with 13 patients (27%) who underwent portovenous resections with R1 resections and 42 patients (24%)

TABLE 1. *Demographic Data on the Patient Population Undergoing Pancreaticoduodenectomy for Pancreatic Adenocarcinoma with and without Portovenous Resections in Conjunction with Length of Stay, Survival, Perioperative Mortality, and In-hospital Mortality*

	Portovenous Resections	Without Portovenous Resections
Patient* (n)	48	172
Age* (years)	67 (67 ± 9.2)	68 (68 ± 7.8)
Gender* (male/female)	27/21	80/92
Body mass index* (kg/m^2)	25 (26 ± 3.6)	26 (26 ± 3.9)
Length of stay* (days)	10, 15 ± 12.9	11, 13 ± 7.7
Survival* (months)	18, 26 ± 26	17, 24 ± 24
Perioperative mortality*	0 (0%)	4 (2.3%)
In-hospital mortality*	2 (4.2%)	5 (2.9%)

* All *P* values were nonsignificant.

without portovenous resections that underwent R1 resections. Residual microscopic disease, however, remained at the pancreatic neck margin (n = 3), bile duct margin (n = 2), pancreatic neck and bile duct margins (n = 1), superior mesenteric artery (SMA) margin (n = 4), peripancreatic lines of resection (n = 2), and at the portal vein margin (n = 1).

Of note, seven (20%) patients requiring portovenous resection to achieve complete tumor extirpation survived longer than 4 years with four patients living to date. No patients who underwent portovenous resections with R1 resections lived 4 years, with the longest survival being 46.5 months *versus* 122.2 months for patients with portovenous resections and R0 resections.

Final staging of the tumors based on pathological examination was Stage IA for 10 patients, Stage IB for 40 patients, Stage IIA for 43 patients, and Stage IIB for 127 patients. These patients are stratified by the need for portovenous resections in Table 3. There was no association between portovenous resections and T stage or nodal status. There was no survival difference between patients undergoing portovenous resections and patients not undergoing portovenous resections even when patients were stratified by T stage, nodal status, or American Joint Commission for Cancer Stage 6th Edition (Table 2).

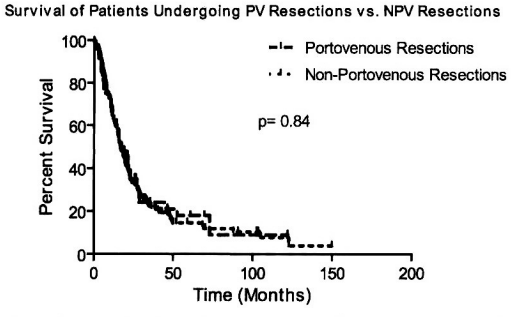

FIG. 1. Survival of patients who underwent pancreaticoduodenectomy with portovenous resections compared with those without portovenous resections. PV, portovenous resection; NPV, no portovenous resection.

The length of stay for patients who did not undergo portovenous resections was not different than those who underwent portovenous resections (11 days, 13 ± 7.7 *vs* 10 days, 15 ± 12.9 days, respectively). All patients who underwent a concomitant portovenous resection survived the perioperative (i.e., 30-day) period, although two patients (4.2%) died in-hospital, one because of a pulmonary embolism and one because of right-sided hepatic necrosis resulting from resection of the right hepatic artery because of contiguous growth of the cancer. Four patients (2.3%) who did not undergo portovenous resections died during the perioperative period and another died in-hospital. None of these five deaths were directly related to the portovenous system (Table 1).

Discussion

The treatment of pancreatic cancer remains inadequate. Resection remains the only hope of cure. Adjuvant chemotherapy improves survival, although marginally. A role for radiation therapy remains to be defined. The hope of prolonged survival and cure, therefore, rests heavily on the shoulders of surgeons. In their efforts to cure patients, surgeons need to strive for

TABLE 2. *Survival Stratified by Margin Status and the Need for Portovenous Resection*

Margin Status	Portovenous Resection	No. of Patients	Survival (months)
R0	Without portovenous resection	130	20, 25 ± 21.9
	With portovenous resection	35	20, 28 ± 29.1
R1	Without portovenous resection	42	13, 21 ± 30.9
	With portovenous resection	13	15, 17 ± 13.1

Survival data are presented as median, mean ± SD.

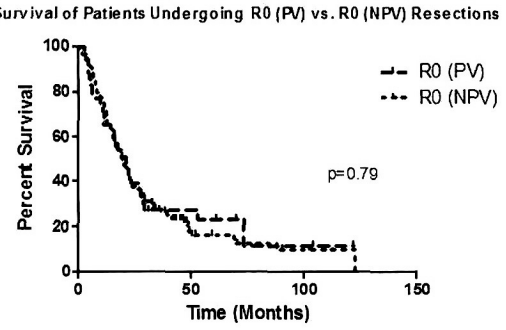

FIG. 2. Survival of patients undergoing R0 resections for pancreatic adenocarcinoma was not negatively impacted by the need for portovenous resections. PV, portovenous resection; NPV, no portovenous resection.

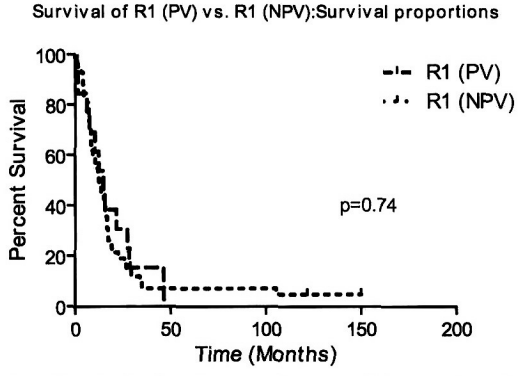

FIG. 3. Survival of patients undergoing R1 resections for pancreatic adenocarcinoma was not negatively impacted by the need for portovenous resections. PV, portovenous resection; NPV, no portovenous resection.

complete tumor extirpation, because complete tumor extirpation yields a significant increase in survival over resections leaving residual microscopic disease. A survival advantage is conferred with portovenous resection by effectively converting an otherwise R1 resection to an R0 resection. Furthermore, we have demonstrated that major portovenous resections can be undertaken to promote prolonged survival and cure without increased perioperative morbidity and mortality.

This is a study of consecutive patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma who were deemed "resectable," or at least not "unresectable," with thorough preoperative evaluations. Our patient population was not gender-biased with the distribution of men and women being nearly equal. The mean age of patients in this study was similar to that reported in other series. Consistent with the disease and our referral practice, patients did not present with "early"-stage cancers; the majority of patients had Stage II disease. Nevertheless, the vast majority underwent complete tumor extirpation. A final pathologic diagnosis of a R0 margin was found in three of four patients and the necessity of portovenous resections did not impart a discernable difference in the incidence of R1 resections. Major portovenous resections necessitate reconstruction to preserve hepatopetal portal blood flow. Reconstruction can include "simple" lateral (transverse) venorrhaphy, more complex end-to-end anastomosis, or most complex interposition grafting using either synthetic graft (unlikely) or autologous vein. Venorrhaphy was undertaken in 44 of 48 patients, indicating focal invasion rather than circumferential venous involvement in the majority of our patients. As well, more complicated venorrhaphy was occasionally undertaken to avoid having to reimplant the splenic vein or other veins (i.e., a large inferior mesenteric vein). Venous encasement requiring interposition grafting or end-to-end anastomosis might represent a different disease process than lateral abutment or involvement of less than 180° of the portovenous structures. Nonetheless, our data strongly support aggressive resection to achieve complete tumor extirpation, particularly because our data show that portovenous resections and reconstructions can be safely undertaken without the need for extensive repairs (i.e., lateral venorrhaphy was the repair most undertaken).

Notable, nearly one in four patients required a portovenous resection in our attempt to provide a R0 resection. The vast majority undergoing portovenous resections had a final pathologic diagnosis of R0. Additionally, those undergoing portovenous resections were approximately equal in distribution between overall R0 and R1 resections undertaken. It has been reported that 6 to 41 per cent of resections for pancreatic adenocarcinoma require concomitant

TABLE 3. *Survival of Patients with or without Portovenous Resections by American Joint Commission for Cancer (AJCC) Stage 6th Edition*

AJCC Stage	Portovenous Resections (no. of patients)	Survival (months)	Without Portovenous Resections (no. of patients)	Survival (months)
Stage IA	0	N/A	10	20, 21 ± 10.7
Stage IB	0	N/A	40	30, 39 ± 32.4
Stage IIA	21	15, 24 ± 31.7	22	17, 22 ± 24.0
Stage IIB	27	22, 27 ± 21.4	100	13, 19 ± 19.0

Survival data are presented as median, mean ± SD.
N/A, not applicable.

portovenous resection.[10, 21] Approximately 20 per cent of the patients in this study underwent portovenous resection, which falls well within this range. This still might seem high, but given that only approximately one-fourth of our pancreatic resections are undertaken for pancreatic adenocarcinoma (rather than intraductal papillary mucinous neoplasms, mucinous cystic disease, cholangiocarcinomas, ampullary cancers, duodenal cancers, extensive ampullary polyps, and so on), only approximately one in 20 pancreaticoduodenectomies in our experience involve a concomitant portovenous resection and reconstruction.

Using length of stay as a surrogate marker, morbidity for patients who underwent portovenous resections was equivalent to those who did not receive portovenous resections. By using length of stay as a surrogate marker, we believe we have captured any major postoperative morbidities (liver failure, myocardial infarction, pulmonary embolism, and so on), because they would invariably extend length of stay. However, this approach does neglect minor postoperative morbidities (atelectasis, urinary tract infections, and so on). The two in-hospital deaths seen in patients undergoing portovenous resections were beyond a 30-day stay in their postoperative period. Neither was directly the result of the portovenous resection. Of note, for the patient undergoing a concomitant right hepatic artery excision and hepatic necrosis, such necrosis is uncommon after unilateral hepatic artery excision. Only 11 per cent of injuries to the right hepatic artery alone result in ischemic necrosis of the right side of the liver, whereas only 14 per cent are associated with hepatic abscess formation.[26]

The patients in our series did not present with "early"-stage cancers. The majority of patients presented with Stage II disease; all of those who underwent portovenous involvement, by definition, were Stage II, because extension beyond the pancreas is criteria for Stage II disease. This is, however, a potential upstaging bias of our study, because our pathologists did not routinely investigate malignant invasion of the portal vein. Pancreatic cancer is associated with an intense desmoplastic reaction, which can be indistinguishable from tumor. Our practice has been to resect tumor adherent to the portal vein or its tributaries en bloc and avoid transection of gross tumor and seeding of the abdominal cavity. It has been determined that, with apparent portovenous invasion, true invasion is present in approximately 39 to 76 per cent.[27–29] Although we acknowledge that microscopic invasion cannot be predicted uniformly in the face of apparent portovenous involvement on preoperative imaging or intraoperative exploration, operative exploration that indicates contiguous growth of the cancer into the portovenous structures should be taken at face value to avoid R1 resections and the poor prognosis they portend. Therefore, resection of the portovenous structures is required to secure the success of complete tumor extirpation. In addition, even when veins are not invaded microscopically by tumor, it can be difficult to separate the peritumoral inflammatory changes from the portovenous structure safely.

Numerous studies support portal vein or superior mesenteric vein resections during pancreaticoduodenectomy.[16–25] However, a recent systematic review in the *British Journal of Surgery* has brought into question the validity of portovenous resections for pancreatic adenocarcinoma, reporting a low subsequent 5-year survival rate, probably, in part, the result of advanced stage with a high rate of nodal metastases.[7] Patients in our study requiring portovenous resection were not more likely to have otherwise advanced staged disease and/or a higher likelihood of nodal metastasis. The majority of our patients had focal portal vein invasion requiring partial vein resection to achieve complete tumor extirpation. In this context, it is not surprising our patients requiring major venous resection to achieve an R0 resection had equivalent survival to patients undergoing R0 resections without portovenous resections. If the portovenous resections can be done safely, an R0 resection is an R0 resection.

R0 resections continue to be the ultimate goal for pancreatic adenocarcinoma, because they consistently prove to lead to improved survival.[24, 25] Portovenous involvement should not preclude resections, especially when R0 margins are possible and when reasonable reconstructions can be achieved. This report supports resection of the portal vein and its tributaries during pancreaticoduodenectomy for pancreatic adenocarcinoma when necessary to achieve an R0 resection.

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DISCUSSION

ALEXANDER A. PARIKH, M.D. (Nashville, TN; Opening Discussion): In the retrospective review of over 200 patients undergoing pancreatic duodenectomy, 48 underwent concomitant portovenous resection. The vast majority underwent lateral venorrhaphy as opposed to interposition graft with circumferential resection, which is rare because most of the studies involve circumferential resection.

There was no difference in overall survival in patients undergoing venous resection *versus* those that did not. Perioperative complications did appear similar. I would like to commend the authors on reporting their margin status and stratifying for both margin status and stage in their study. This resulted in no difference in their overall survival. The 25 per cent R1 positive margin rate is very reasonable when compared with other multi-institution and single-institution reports and again speaks of the quality of their resections.

Originally described by Fortner over 30 years ago as part of an extended pancreatic resection, resection of the portovenous structures during pancreaticoduodenectomy has undergone significant improvements as has been shown in several contemporary reports. Venous resection during the pancreaticoduodenectomy is safe and leads to similar and, perhaps, improved survival rates when compared with those not undergoing a venous resection when you control for margin status and stage.

The study further supports these recommendations that if resection of the SMV and portal vein is required through lateral resection or circumferential with either primary repair or a graft and that is what is required to obtain negative margins, then this should be done. This may provide the only long-term cure in these patients.

The authors mentioned a collective report published in 2006 by Siriwardana and colleagues in the *British Journal of Surgery*. This report is a collective review of 1600 resections done over a 40-year period and somewhat questions the validity of this aggressive approach. I would like to caution, however, that this study has several issues. In over 40 years and 1600 patients, there was very little quality control in terms of margin status, no stratification, and a low survival rate of 13 mean months and the high margin-positive rate is

not consistent with most modern literature. Therefore, concerning the wealth of literature supporting the resection of the portal vein, I do not think we should be swayed by a single collective review.

The authors mention that intraoperative frozen sections were obtained to confirm negative margins and additional resections were undertaken to achieve margins if possible. What margins were frozen? How was the retroperitoneum margin evaluated and was the vein margin confirmed as negative in the operating room?

In 50 to 80 per cent of the time, the vein is actually involved with the cancer. In your study, was the vein margin looked at pathologically, and what percentage was actually invasion?

For patients with expected venous involvement by preoperative imaging, was there consideration of neoadjuvant strategies before resection as several reports have suggested? If not, when would you suggest that preoperative therapy be used before this resection?

DAVID FELICIANO, M.D. (Nashville, TN): This is one of the highest incidences of venous resection I have ever seen in any paper on Whipple's. It begs the question, are the authors ignoring their preoperative imaging? Are they doing intraoperative staging? If they feel it is not completely resectable, are they still going ahead and doing it? This is way, way out there. I would like to hear what the philosophy is of Dr. Rosemurgy's group on why they are doing this.

Everything is not about the margin in Whipple's. It is also about the nodes. John Cameron's group has clearly shown that if you have negative nodes, you will live 4 years. If you have positive nodes without chemotherapy, you are dead in 12 months. Tell us how you broke out the nodes in all those subgroups.

CHUCK SCOGGINS, M.D. (Louisville, KY): Did you have the opportunity to look at the other therapies given to these patients such as chemotherapy and radiation? Does this correlate with survival?

MARK MITCHELL, M.D. (Jackson, MS): In my experience, there are two types of patients, the ones where you know you may be going after the portal vein preoperatively, and on those patients, I am given a heads up on. In the other patient group, it is an unanticipated intraoperative decision. Is there a difference in survival between those two groups?

RUSSELL HOWERTON, M.D. (Winston-Salem, NC): Tell us more about the location of the positive margins in the R1 patients with portal vein resection. Was that in an area remote and not your main path to the portal vein resection such as posterior in the uncinate near the SMA or was that related to the vein resection?

PAUL TOOMEY, M.D. (Tampa, FL; Closing Discussion): We routinely obtain frozen sections of the common bile duct and pancreatic duct margins. All other frozen sections are obtained at the discretion of the operating surgeon when there is a high suspicion for tumor involvement.

Approximately 40 to 50 per cent of true invasion has been shown to involve the actual portal vein when seen by the pathologist after portal vein resection. R0 resections are the ultimate goal, regardless of having involvement of the portovenous structures. You cannot decide that preoperatively. You cannot determine which patients preoperatively are going to have pathologic invasion of the portal vein.

Regarding neoadjuvant therapy, we have an aggressive approach to surgical therapy, and very few patients undergo neoadjuvant therapy, unless they are under one of our studies. None of our patients in this study underwent neoadjuvant therapy.

Regarding the high incidence of portal vein resections, I think it has to do with our patient population. We have a highly referral-based center. It is a high-volume center, and this does increase the amount of complexities that are sent to us. I think that has a large impact into the amount of portovenous resections that we do.