Radical Antegrade Modular Pancreatosplenectomy Procedure for Adenocarcinoma of the Body and Tail of the Pancreas: Ability to Obtain Negative Tangential Margins

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BACKGROUND: Positive resection margins and low lymph node counts are common in resections of cancers of the body and tail of the pancreas. In 2003, we described a novel approach for resection of the pancreas called radical antegrade modular pancreatosplenectomy (RAMPS), which was directed toward these problems. We now present results of treatment of patients with adenocarcinoma using RAMPS with particular reference to the ability of this procedure to obtain negative tangential margin rates.

STUDY DESIGN: Data from 23 patients treated with RAMPS procedure were collected in a prospective database. Data from the operative notes, pathology reports, and postoperative data were entered into the database.

RESULTS: Mean (±SD) operative time was 6.3 (±1.8) hours. Fifteen patients had anterior RAMPS procedure and eight posterior RAMPS procedure. There were no postoperative (30 days) or hospital deaths. Eighteen postoperative complications developed in 12 of 23 (52%) patients. Mean tumor size was 5.1 cm. Invasion outside the pancreatic capsule was identified in 78% of patients. Median number of nodes was 15. Ninety-one percent had negative tangential margins, which is the main finding of the study. Median survival was 21 months. The 5-year overall survival is 26%, but followup is still short.

CONCLUSIONS: RAMPS procedure can achieve negative tangential margins in a high percent of patients with resectable carcinoma of the body and tail of the pancreas. Median and overall survival rates are quite satisfactory for this tumor and are similar to rates reported for the Whipple procedure.
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Adenocarcinoma of the body and tail of the pancreas is notable for having a high rate of recurrence after resection.[1-4] The traditional approach of left-to-right pancreatosplenectomy is associated with a high positive tangential margin rate and is not based on the described lymph node drainage of the organ. In 2003, we described a novel approach for resection of this part of the pancreas called radical antegrade modular pancreatosplenectomy (RAMPS).[1] This procedure is modular in that the plane of the posterior dissection can be directly on the left adrenal gland and Gerota's fascia (anterior RAMPS) or can be posterior to the adrenal and Gerota's fascia (posterior RAMPS), depending on the extent of penetration of the tumor on CAT scan. The dissection commences from right-to-left with early division of the neck of the pancreas and splenic vessels and a celiac node dissection. From there, the plane of dissection runs posteriorly in a sagittal plane along the superior mesenteric artery and celiac artery to the level of the aorta and then laterally either anterior or posterior to the adrenal. The purpose of this article is to present results for patients with adenocarcinoma of the pancreas treated with this procedure, with special reference to the ability of the procedure to obtain negative tangential margin rates.

Competing Interests Declared: None.

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METHODS

RAMPS procedure has been described in detail previously.[1] A staging laparoscopy is performed to rule out

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peritoneal or liver metastases. RAMPS procedure is usually performed through a left-sided upper abdominal J-incision. The lesser sac is entered and the neck of the pancreas is elevated off the superior mesenteric and portal veins. The right gastric artery is divided and the lesser omentum opened. A celiac node dissection is performed, during which the celiac artery and its three branches are exposed. The neck of the pancreas is divided. Currently, a sheathed stapler (Seamguard; WL Gore & Assoc) is used for this purpose, although during the course of this study, unsheathed staplers or sharp transection and sutures were used on some patients. The splenic artery is ligated and divided close to its origin and the splenic vein is divided with a vascular stapler close to its termination. The plane of dissection then proceeds vertically in the sagittal plane, exposing the left side of the celiac and superior mesenteric arteries down to the level of the aorta. The left renal vein is exposed where it passes behind the superior mesenteric artery and in front of the aorta. Performing a Kocher maneuver and identifying the left renal vein from the right side can help to identify it in the base of the dissection on the left side. If an anterior RAMPS procedure is to be performed, the adrenal vein is followed onto the adrenal and then more laterally the dissection proceeds to the left, directly on Gerota's fascia. When a posterior RAMPS is needed, the adrenal vein is divided at its union with the renal vein and the dissection proceeds posterior to the adrenal and then more laterally behind Gerota's fascia directly onto the surface of the kidney. The renal vein marks the inferior extent of the dissection and the diaphragm the superior extent. The short gastric vessels are divided, as are the splenocolic and lienorenal ligaments, and the specimen is removed. When tumors invade into the stomach, mesocolon, colon, or small intestine, these structures can be resected, as in the standard method. Renal involvement is uncommon, but the method described allows resection of the kidney with long lengths of its vessels, if necessary. Resection of portions of the superior mesenteric and portal vein is possible, as in the case of a Whipple procedure.

Pancreatic transection margin and all tangential margins on the specimen were inked in the operating room once the specimen was removed to the back table. All surfaces of the specimen not covered with peritoneum were inked, ie, the posterior surface and the superior and inferior edges. The resection margin at the neck of the pancreas was also inked and sent for frozen section. The peritonealized anterior surface of the pancreas, ie, the posterior surface of the lesser sac, was not inked, and tumor penetration of the anterior peritoneum without involvement of an adjacent organ was not considered a positive margin. When an adjacent organ was resected, the resection margin on that organ was inked.

Patients with adenocarcinoma of the pancreas, treated with RAMPS, were collected in a prospective database from Washington University in St Louis/Barnes-Jewish Hospital. Data from operative notes, pathology reports, and postoperative data were entered into the database. A Kaplan-Meier survival curve was calculated by standard methods. Median length of followup was calculated from patients still alive at the time of analysis.[2] Complications were graded by Zurich modification of the University of Toronto classification of complications.[3,4] A pancreatic fistula was defined as drainage of $\geq$ 50 mL fluid from a drain on day 10 or later, with amylase concentration of $\geq$ 500 IU or radiologic demonstration of a fistula.

RESULTS

Patients

There were 23 patients with adenocarcinoma of the pancreas treated from June 1999 to November 2004. One patient had associated intraductal papillary mucinous tumor and, in another, the solid tumor appeared to be arising in a cyst. Patients with neuroendocrine tumors and rare malignant tumors of the pancreas were excluded from this presentation. The patient group included 13 women and 10 men; average age was 65 years.

Twenty patients presented with symptoms attributable to the cancer; three cancers were found incidentally on imaging for another condition, such as gastroesophageal reflux disease. The main presenting symptom was pain in 17 patients, anemia in 2, and weight loss in 1. The location of pain was epigastric, left flank, or back, or a combination of these sites. Fifteen patients had weight loss ranging from 3 to 50 lb and four patients had signs of acute pancreatitis. Other symptoms included new onset constipation in four patients and nausea and vomiting in two patients. Preoperative staging was by pancreas protocol CAT scan using oral and IV contrast with fine-cut images obtained before contrast injection and in the arterial and venous phases. (18)F-fluorodeoxyglucose positron emission tomography scan was not used in preoperative staging. Two patients had neoadjuvant chemotherapy.

Operative procedure

Mean (±SD) operative time was 6.3 (±1.8) hours. Estimated blood loss was 630 (±518) mL. Range of blood loss was 150 mL to 2,500 mL. Four (17%) patients received between 2 and 5 U packed red blood cells during the procedure. Fifteen patients had an anterior RAMPS procedure and eight had posterior RAMPS procedure. In total, 15 of 23 (65%) patients had an adjacent structure or organ resected. In addition to the adrenal, 19 other intraabdominal structures were resected en bloc with the pancreas because of adherence to the tumor or invasion by it. Additional procedures required were resection of the transverse mesocolon (six patients), total or partial gastrectomy (five patients), partial colectomy (three patients), partial or total nephrectomy (two patients), resection and reconstruction of superior mesenteric and portal veins (two patients), and resection of portion of diaphragm (one patient).

There were no postoperative (30 day) or hospital deaths. A patient who was discharged after an unremarkable 8-day postoperative course died 6 weeks after operation after a brief admission to the emergency ward of an outside hospital. The cause of death was unclear. Eighteen postoperative complications developed in 12 of 23 (52%) patients. Type and grade of complications are listed in Table 1. There were no grade 1 complications recorded. The lack of such complications, which are usually corrected by minor bedside procedures, is probably a result of inadequate recording. There were no pancreatic fistulas in this group, but an intraabdominal abscess developed in one patient and two others had fevers of unknown origin, which responded to antibiotics. These problems were likely a result of leaks at the pancreatic closure. Median length of stay was 11 days (range 5 to 40 days).

Table 1. Postoperative Complications

Grade 2	
Fever of unknown origin	2
Tachycardia	2
Leg vein thrombosis	2
Prolonged ileus	2
Line sepsis	1
Clostridium difficile colitis	1
Calf vein thrombosis	1
Troponin elevation	1
Urinary tract infection	1
Pyelonephritis	1
Grade 3	
Intraabdominal abscess	1
Abnormal LFTs requiring percutaneous cholangiogram	1
Grade 4a	
Line sepsis requiring ICU admission	1
Bleeding DU requiring ICU admission	1

DU, duodenal ulcer; LFT, liver function test.

Pathologic examination of resected specimen

Tumors ranged in size from 1.4 to 14 cm with mean (±SD) size of 5.1 (±2.6) cm. Median size was also 5 cm. Invasion outside the pancreatic capsule into peripancreatic soft tissues was identified in 18 of 23 (78%) patients, ie, 18 of 23 patients had T3 tumors and the other 5 were T2. Four of eight (50%) patients who had posterior RAMPS procedure had direct invasion of the adrenal gland, another had "invasion of tissues around the adrenal gland," and the other three had penetration of the posterior capsule of the pancreas with soft tissue invasion only. The spleen was directly invaded in four patients. The colon and kidney were directly invaded by tumor in the patients in whom they were resected. The stomach was directly invaded in three of five patients in whom a gastrectomy was done; in one patient there was perigastric cancer and in one patient there were inflammatory adhesions only. The diaphragm was directly invaded by tumor in the one patient in whom resection was performed. The pathology reports make no specific mention of the state of the mesocolon or vein when these resections were done. The lymph node count in the specimen ranged from 1 to 29, with a mean (±SD) of 14.3 (±7.8) nodes. Median number of nodes was 15 and the patient in whom only 1 node was recovered had had neoadjuvant chemoradiation. Eleven of 23 (48%) patients had between one and five lymph nodes positive for malignancy (N1), and 12 (52%) had no positive lymph nodes (N0). Twenty-one patients were M0, but two patients with T3 tumors were found to have a small focus metastatic tumor in the pathologic specimen (M1). American Joint Commission on Cancer stage groups were stage IA: no patients, stage IB: three patients, stage IIA: nine patients, stage IIB: nine patients, stage III: no patients; and stage IV: two patients. Tumors were well differentiated, moderately differentiated, and poorly differentiated in 1, 12, and 8 patients, respectively, and in 2 the grade was not given. Of 11 patients for whom it was commented on, 9 had either perineural or microvascular invasion. One tumor, as noted previously, was associated

with intraductal papillary mucinous tumor and one tumor appeared to be arising in a cyst.

Three patients had positive margins. One patient had a positive microscopic margin in the transection plane at the pancreatic neck in permanent histologic sections after having a negative frozen-section margin. Two patients had positive tangential margins despite having a posterior RAMPS procedure. Both had extensive extrapancreatic disease with direct invasion by the cancer of the adrenal, stomach, and diaphragm in one patient, and the adrenal, spleen, and stomach in the other.

Twenty of 23 (87%) patients had negative margins and 21 of 23 (91%) had negative tangential margins.

Followup

Mean and median followup time of living patients is 25 and 17 months, respectively. Four patients required nutritional supplementation at home for weeks to months after operation, either as total parenteral nutrition or gastrointestinal tube feedings, because of their failure to thrive on oral intake. Fifteen patients had adjuvant chemoradiation in addition to two patients who had neoadjuvant chemoradiation.

Eleven patients are alive without evidence of disease. Twelve patients have died, including the patient who died of unknown cause 6 weeks after operation. Eleven patients died within months of being diagnosed with recurrence. The site of recurrence is known in nine patients and unknown in two. Six of nine (66%) had local recurrence in the abdomen. Metastatic disease developed in five of nine (55%) patients; three had liver metastases, and three had metastases in other sites (one patient had liver and bone metastases). Two of nine patients had both local recurrence and distant metastases at the time that recurrence was initially detected. Death occurred 3 to 45 months after operation in these patients (mean 15 months). Overall survival curve is shown in Figure 1. Median survival was 21 months. Five-year overall survival is 26%. Because all patients who recurred have died, this is also the current figure for 5-year disease-free survival. Median followup time of living patients is short, which is a reflection of the increased use of the procedure in our institution since 2003. If the two patients with adenocarcinoma arising in a cystic diseases of the pancreas are removed, the 5-year overall survival in the remaining 21 patients is 21%.

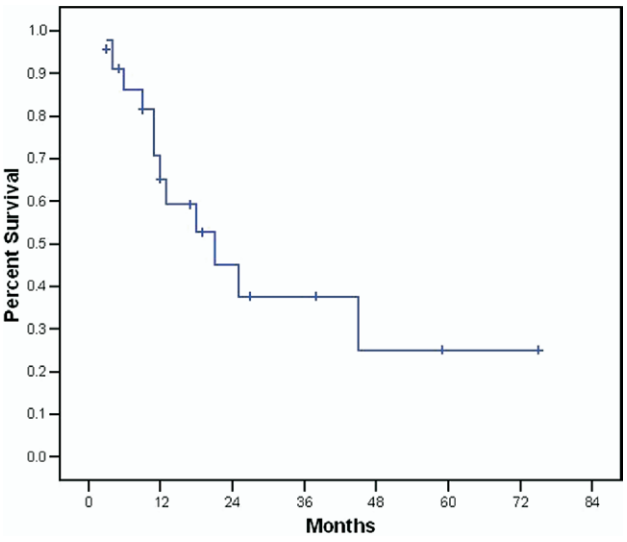

Figure 1. Overall survival in 23 patients treated with the radical antegrade modular pancreatosplenectomy procedure.

DISCUSSION

Recurrence after surgical resection of cancers of the body and tail of the pancreas is very common and survival rates remain low, even in expert hands.[5-8] In part, this is because of the aggressive nature of this malignancy. It might also be attributable to the frequent failure of the usual surgical approaches to obtain the basic goals of an oncologic surgical resection—negative margins and N1 node dissection. Much effort has gone into refinement of the Whipple procedure, in an attempt to routinely obtain the basic surgical goals of the procedure. Resection of the body and tail of the pancreas, which is a much less commonly performed procedure for invasive cancers, has received considerably less attention. The standard left-to-right procedure performed unchanged for 100 years has many conceptual and practical shortcomings. Chief among these is the lack of a clear concept of where the posterior plane of dissection should lie in principle and how this principle should be practically achieved in specific patients. Additional shortcomings are failure of the dissection to remove all N1 nodes, late control of blood supply, and poor visibility of dissection planes when moving from left to right. RAMPS procedure was designed to eliminate these problems. We have previously discussed how RAMPS dealt with these additional shortcomings in detail,[1] but some consideration of the posterior dissection plane is in order, as obtaining negative posterior margins in resections for adenocarcinoma is the major issue of this presentation.

RAMPS selects one of two posterior planes of dissection, based on the position of the tumor in the pancreas. The more superficial plane of the anterior RAMPS procedure lies directly on the surface of the left adrenal gland and Gerota's fascia. This plane is accurately and reproducibly established by identification of the adrenal vein as a tributary of the renal vein. The en bloc dissection mass is lifted off the adrenal vein until the surface of the adrenal is reached and cleared. The same is difficult to achieve reproducibly in a left-to-right dissection, as there is no indicator of the left border of the adrenal and the plane of dissection tends to be on the posterior surface of the pancreas rather than the anterior surface of the adrenal. In the posterior RAMPS procedure, the plane of dissection is the posterior abdominal wall and the surface of the kidney, and exceptionally part or all of the left kidney can be removed. The decision to perform an anterior versus a posterior RAMPS procedure is made preoperatively using a fine-cut three-phase CAT scan. When a rim of normal pancreas remains posterior to the tumor, the anterior RAMPS is chosen; when the posterior margin of the tumor contacts or appears to break through the posterior capsule of the pancreas, the posterior RAMPS is selected. RAMPS establishes, in principle, where the posterior plane of dissection should lie and provides a method to determine that plane in individual patients. Using this approach to the posterior resection margin, combined with resections of adjacent organs and tissues in $>$ 50% of patients (65% if the adrenal is included), we were able to obtain negative tangential margins in 21 of 23 (91%) patients. This was possible despite the fact that there was invasion of tissues outside the pancreatic capsule in 78% of patients.

There are very few literature studies on this subject in which margin rates and survival rates are reported. Shoup and colleagues[5] (Memorial Sloan Kettering) reported on 57 patients who had resection of adenocarcinoma of the pancreas over 17 years (1983 to 2000). Standard resection, defined as resection of pancreas and spleen only, was performed in 61% of patients and extended resection, defined as resection of an adjacent organ, was performed in the remaining 39% of patients. Frequency of resection of the left adrenal is not given. Forty-one of 57 (72%) patients had negative margins and 16 of 57 (28%) had positive margins. It is not stated whether specimens were routinely inked or where positive margins were detected on the specimen. Number of nodes in resected specimens was not stated. Margin positivity was not statistically significantly associated with poorer survival, but lymph node positivity, present in 48% of patients, was associated with poorer survival. Median survival, reported as "disease-specific survival" was 16 months and 5-year survival was about 15%. Christein and colleagues[6] (Mayo Clinic) reported on 93 patients treated over a 16-year period (1986 to 2003). Twenty-seven had carcinomas arising in cystic diseases of the pancreas and 66 had ductal adenocarcinoma. An en bloc resection defined as a resection of an adjacent organ was performed in 35% of all patients, and in 39% of those with ductal adenocarcinoma. The adrenal was resected in four patients. Eighty-three percent had negative margins, but tangential ("radial") margins were reported in only 62% of specimens. The negative margin rate fell to 73% in patients who had an adjacent organ resected. No lymph nodes were identified in 15% of specimens, and the number of nodes resected in the other patients is not stated. Thirty percent of patients had positive lymph nodes. Median survival in the 66 patients with ductal adenocarcinoma was 16 months and 5-year survival rate was about 5%. A different approach was described by Shimada and colleagues[7] (National Cancer Hospital), who reported on 88 patients with ductal adenocarcinoma treated over 15 years (1990 to 2004). Seventy-six underwent an operation in which the posterior margin was essentially that of a posterior RAMPS, ie, the left adrenal and Gerota's fascia were routinely resected. The remaining 12 patients underwent an "Appleby procedure,"[8] in which the celiac artery and common hepatic artery and stomach were also resected. This suggests that this series contains patients with more locally advanced cancer than in the American series, including our own. An N3 node dissection was also routinely performed. The N2 node group described by Shimada and colleagues is routinely dissected in a RAMPS procedure because, according to O'Morchoe,[9] these nodes are N1 for the central part of the pancreas, but an N3 dissection (para-aortic dissection from IVC to left gonadal vein and from crus down to internal mammary artery origin) is not done in RAMPS. Sixty-six of 88 (75%) patients had negative margins and 22 of 88 (25%) had positive margins. The number of patients with positive margins in their standard procedure versus the Appleby procedure is not stated. Inking is not described nor is the site of margin positivity. Patients with negative margins had a median survival of 39 months versus 17 months for those with positive margins. The

number of nodes resected is not given, but 78% of patients had positive nodes. Node positivity was statistically significantly related to decreased survival. The number of patients who had adjacent organs resected other than the adrenal (resected routinely) and stomach (resected in the Appleby operation) is not given. Median survival was 22 months and 5-year overall survival rate was 19%. None of the 12 patients who underwent the Appleby procedure survived longer than 2 years, nor did any of the patients with N2 or N3 node involvement. Poor outcomes after N3 node dissection have been reported previously.[10]

It is not possible to compare the different series in a way that permits confident conclusions. One problem is that there is not a standard reporting schema. Several modest conclusions seem possible from our own results and the published studies discussed previously. The modular approach of RAMPS based on high-quality CAT scans done in the immediate preoperative period seems to achieve a high rate of negative margins without routine resection of the adrenal gland and Gerota's fascia, as performed by Shimada and colleagues.[7] Shimada's results indicate that the Appleby operation should be performed very selectively, if at all, in an attempt to resect T3 disease, which abuts the celiac artery.[7] Similarly, N3 node dissection seems to be of no value in the treatment of this disease (whether in the body or head of the pancreas) and routine resection of the adrenal and Gerota's fascia does not seem to improve results.[7] To be able to compare results, a standard method of inking specimens in the operating room is highly desirable. The method used in this study seems appropriate.

RAMPS is a lengthy operation, adding about 30 to 60 minutes to the standard procedure. About 50% of patients will have a complication of grade 2 or higher. Additionally, about 25% of patients have had a prolonged recovery with poor appetite and poor food intake requiring supplemental nutrition for several months. This might be related to the resection of nerves along the superior mesenteric and celiac arteries.

In summary, RAMPS procedure can achieve negative tangential margins in a high percent of patients with resectable carcinoma of the body and tail of the pancreas. Median and overall survival rates are satisfactory for this type of tumor and are similar to rates reported for the Whipple procedure. We believe that this approach should be adopted as the standard method for the present time.

Author Contributions

Study conception and design: Strasberg, Linehan
Acquisition of data: Strasberg, Linehan, Hawkins
Analysis and interpretation of data: Strasberg, Linehan, Hawkins
Drafting of manuscript: Strasberg, Linehan, Hawkins
Critical revision: Strasberg, Linehan, Hawkins

REFERENCES

1. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery 2003;133:521–527.
2. Bollschweiler E. Benefits and limitations of Kaplan-Meier calculations of survival chance in cancer surgery. Langenbecks Arch Surg 2003;388:239–244.
3. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992;111:518–526.
4. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. [comment in: Ann Surg 2004;240(2):214−215].
5. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastrointest Surg 2003;7:946–952.
6. Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. J Gastrointest Surg 2005;9:922–927.
7. Shimada K, Sakamoto Y, Sano T, Kosuge T. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. Surgery 2006;139:288–295.
8. Kimura W, Han I, Furukawa Y, et al. Appleby operation for carcinoma of the body and tail of the pancreas. Hepatogastroenterology 1997;44:387–393.
9. O'Morchoe CC. Lymphatic system of the pancreas. Microsc Res Tech 1997;37:456–477.
10. Nakao A, Harada A, Nonami T, et al. Lymph node metastasis in carcinoma of the body and tail of the pancreas. Br J Surg 1997; 84:1090–1092.