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Intraoperative Radiation Therapy Following Pancreaticoduodenectomy

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Objective

To determine the morbidity and mortality of pancreaticoduodenectomy followed by electron-beam intraoperative radiation therapy (EB-IORT).

Summary Background Data

Local recurrence following pancreaticoduodenectomy occurs in 50% to 90% of patients who undergo a potentially curative surgical resection for adenocarcinoma of the pancreatic head. To improve local disease control, a more aggressive retroperitoneal dissection has been combined with adjuvant EB-IORT.

Methods

Forty-one patients with malignant neoplasms of the periampullary region underwent pancreaticoduodenectomy followed by EB-IORT between January 1989 and May 1992. EB-IORT was delivered in a dedicated operative suite, eliminating the need for patient relocation. Electron-beam energies of 6 to 12 MeV were used to deliver 10 to 20 Gy to the treatment field following resection but before pancreatic, biliary, and gastrointestinal reconstruction.

Results

Median operative time was 9 hours, blood loss was 1 L, perioperative transfusion requirment was 2 units, and hospital stay was 20 days. One patient died of a postoperative myocardial infarction, and four patients required reoperation, one for an anastomotic leak. No patient failed to receive EB-IORT because of operative complications during the time period of this study.

Conclusion

Adjuvant EB-IORT after pancreaticoduodenectomy can be delivered safely, with low mortality and acceptable morbidity.

Current surgical treatment for adenocarcinoma of the pancreatic head is based on the surgical procedure of pancreaticoduodenectomy as first described by Whipple et al.[1] However, because of tumor recurrence in the liver, peritoneum, and the bed of the resected pancreas, surgery alone cures no more than 25% of patients who undergo resection.[2-5] In fact, local recurrence has been documented in 50% to 90% of patients after pancreaticoduodenectomy.[6-10] Attempts to improve local control and survival by performing extended lymphatic resection have met with conflicting results[8,11-14] and have been associated with unacceptable morbidity and mortality in some centers.[15-17] In a series from Japan, extended resection did not prevent local recurrence unless combined with intraoperative irradiation.[13-14]

Encouraged by the limited Japanese experience and the effectiveness of electron-beam intraoperative radiation therapy (EB-IORT) in controlling local disease in patients with unresectable locally advanced adenocarcinoma of the pancreas,[18-21] we combined adjuvant EB-IORT with a more extensive retroperitoneal dissection as a strategy to improve local disease control in patients with potentially resectable pancreatic cancer.[22] Until now, little has been reported on the effects of post-pancreaticoduodenectomy irradiation of the retroperitoneum encompassing the superior mesenteric vein–portal vein confluence (SMV–PV), inferior vena cava (IVC), aorta, superior mesenteric artery (SMA), and hepatic artery.[14,17,23,24] Here, we report the perioperative morbidity and mortality in the largest single-center study of pancreaticoduodenectomy followed by EB-IORT for malignant neoplasms of the periampullary region.

PATIENTS AND METHODS

Forty-one patients underwent pancreaticoduodenectomy followed by EB-IORT between January 1989 and May 1992. Laparotomy with biopsy and/or biliary or gastric bypass had been performed at other institutions in 19 patients prior to referral. Patients received a full explanation of the purpose, procedures, and risks of EB-IORT and signed a statement of informed consent.

EB-IORT was delivered in a dedicated operating suite, making patient relocation unnecessary. All patients' malignancies were cytologically or histologically confirmed before delivery of EB-IORT. Patients with completely resected neuroendocrine tumors and microscopically negative margins of resection were not treated with EB-IORT.

Twenty-four patients were treated as part of a protocol consisting of preoperative external-beam radiation therapy (45 to 50.4 Gy given in 1.8-Gy fractions on Monday through Friday) and concomitant protracted-infusion 5-fluorouracil (5-FU; 300 mg/m^2/day).[25] Eight of the remaining 17 patients received postoperative radiation therapy and concomitant 5-FU.

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Equipment

The Siemens Mevatron ME (magnetron, electrons only) (Siemens Medical Laboratories, Inc., Concord, CA) is the first linear accelerator designed for dedicated electron intraoperative radiation therapy within the operating room. It consists of a wall-mounted isocentric gantry with power and control cabinets located in an adjacent room. Radiofrequency energy is generated by a high-power magnetron that can accelerate an electron beam to energies between 6 and 16 MeV. The Mevatron ME can treat at a dose rate of 900 cGy/min to minimize treatment time. The linear accelerator was attached to a 50-cm–thick concrete wall; the other walls were lined with 1.3 cm of lead as previously described.[26]

The Mevatron ME uses chrome-plated brass treatment cones with diameters of 5 to 12 cm and straight or beveled ends. The cone used is optically aligned with a laser projection system and is firmly attached not to the treatment collimator but rather to the surgical table using a modified Bookwalter retractor (Codman and Shurtleff, Inc., Randolph, ME).[27] The surgical table, used for both the operative procedure and patient positioning under the linear accelerator, is a modified Marquet Hiedlberg S couch (Marquet International, Rastatt, Germany). Modifications necessary to allow laser cone alignment include: swivel wheels at both ends of the couch base for ease of mobility; lead screws with hand cranks to provide longitudinal and lateral motion of the table surface; and a covered hand control to prevent folding motions of the table.

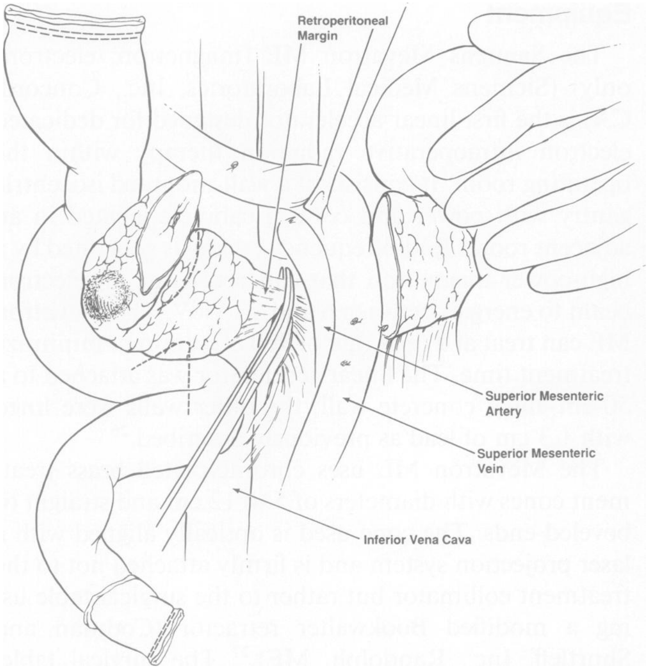
Dosimetry measurements were made for each combination of energy, cone diameter, and cone type (straight or beveled). From these data, depth-dose curves, cone output factors, and air-gap correction factors were produced that allowed the calculation of monitor settings for delivering a prescribed dose at any selected treatment depth.[28] Doses of EB-IORT were prescribed to the 90% isodose depth.

Surgery and Intraoperative Radiation Therapy

All surgical resections were performed under the direction of two faculty members (DBE, FCA). As previously described,[29] our operative procedure differs from a standard pancreaticoduodenectomy in three major areas:

1. A wide Kocher maneuver is performed to remove all lymphatic tissue over the medial aspect of the right kidney, IVC, and left renal vein. Often in reoperative cases this plane has not been previously entered.

2. A wide retroperitoneal dissection is performed with complete exposure of the SMA and ligation of the inferior pancreaticoduodenal artery. After pancre-



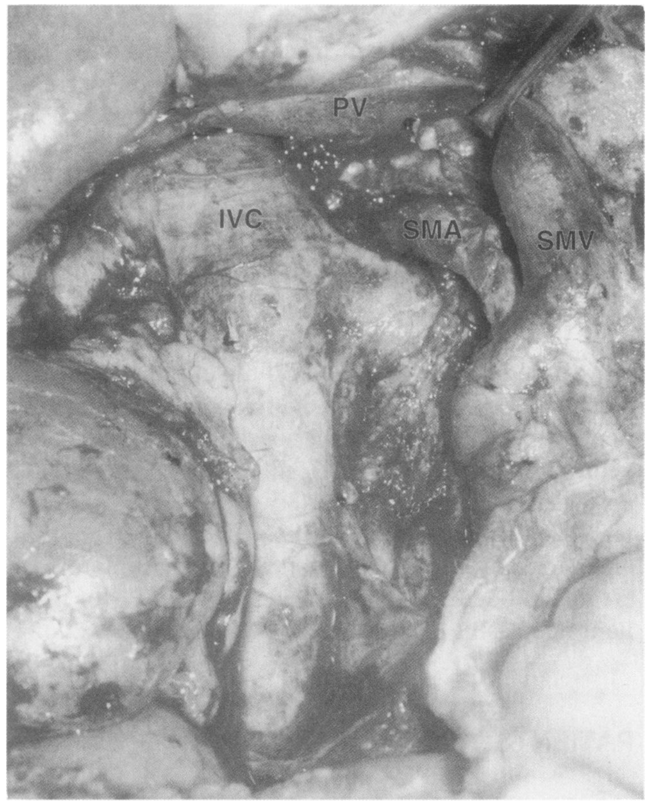


Figure 1. (A, left) The final step in pancreaticoduodenal resection. The SMV–PV confluence is fully mobilized and retracted medially allowing exposure of the SMA. The retroperitoneal margin is identified as the tissue adjacent to the SMA origin. (B, right) After tumor removal, the SMV–PV confluence is retracted medially revealing the extent of dissection along the SMA.

atic transection, the SMV–PV confluence is completely mobilized off the uncinate process of the pancreas and retracted medially to the patient's left, allowing exposure of the SMA approximately 6 to 8 cm from its origin. The specimen is separated from the SMA using sharp dissection in a distal to proximal direction. The tissue adjacent to the proximal 3 to 4 cm of SMA is labeled as the retroperitoneal margin (Fig. 1).

3. Segmental resection of the SMV–PV confluence is performed when the tumor is inseparable from the lateral wall of the vein. By transecting the splenic vein, the specimen and attached SMV–PV confluence can be retracted laterally, allowing exposure of the SMA medial to the SMV. The retroperitoneal dissection along the SMA is then completed, leaving the specimen attached only by the SMV–PV confluence. A segmental vein resection with primary end-to-end anastomosis is then performed with 6-0 prolene suture (Fig. 2). This results in cephalad displacement of the root of mesentery toward the hepatic hilum, often reducing the diameter of the IORT field.

The retroperitoneal margin was identified by the operative surgeon and subjected to en-face frozen section histologic review. When tumor was within 2 mm of the cut surface, the margin was interpreted as positive. The common bile duct and pancreatic transection margins were also subjected to frozen section analysis. The common bile duct and pancreas were resected until negative margins were obtained.

The dose of EB-IORT delivered was based on the histology of the retroperitoneal margin: 10 Gy when negative, 15 Gy when microscopically positive, and 20 Gy when grossly positive.

The EB-IORT treatment field included the retroperitoneum and tumor bed extending from the transected bile duct superiorly, to the right kidney laterally, and to the pancreatic remnant medially (Fig. 3).[22,30] The bile duct and pancreatic remnant were excluded from the treatment field. The sides of the treatment cone prevented the gastric remnant, small bowel, and colon from entering the treatment field. Extrinsic cone compression of the SMV–PV confluence and IVC was avoided by careful cone placement. EB-IORT fields ranged from 5 to 10 cm in diameter.

All patients received early postoperative enteral feeding through a jejunostomy tube. Patients were discharged when they could tolerate prolonged clamping of their gastrostomy tube. Most patients were discharged while still receiving enteral tube feedings and advanced

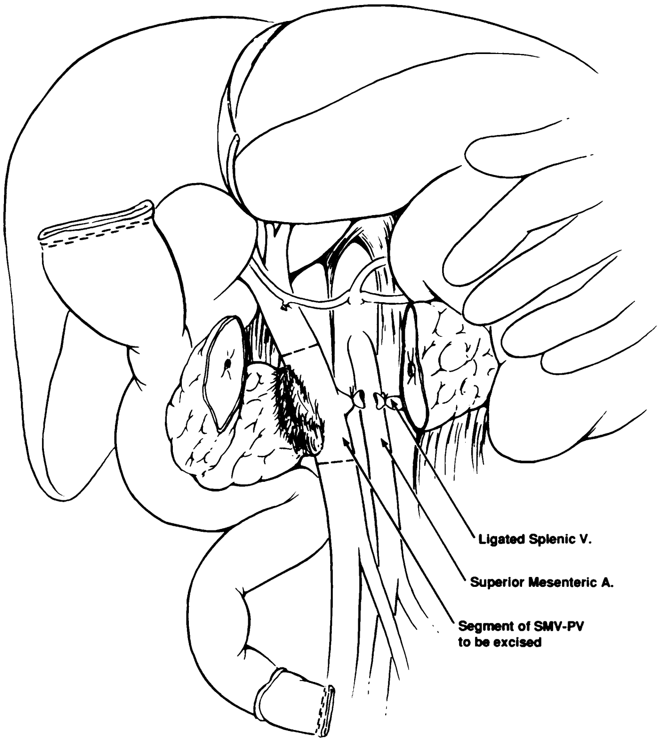


Figure 2. The final step in pancreaticoduodenectomy when segmental resection of the SMV-PV is required because of direct venous invasion. The splenic vein is ligated and divided, allowing exposure of the SMA medial to the SMV and completion of the retroperitoneal dissection. The SMV-PV is then divided, the specimen removed, and a primary end-to-end anastomosis completed.

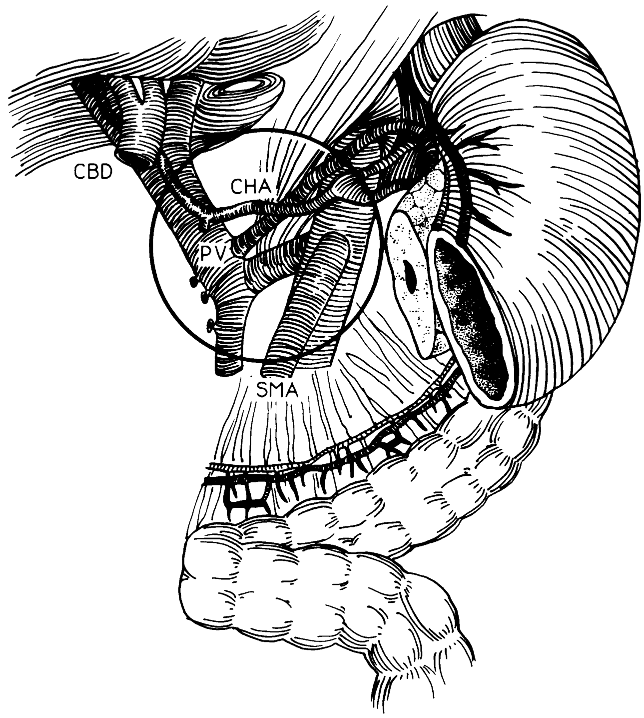


Figure 3. The EB-IORT treatment field included in the circular chrome-plated brass treatment cone. CBD: common bile duct; CHA: common hepatic artery. Adapted with permission from Evans DB, Byrd DR, Mansfield PF. Preoperative chemoradiotherapy for adenocarcinoma of the pancreas: rationale and technique. Am J Clin Oncol 1991; 14:359–364.

their oral diet as outpatients under the direction of a clinical dietitian.

RESULTS

Patient and Treatment Characteristics

The 41 patients (21 men and 20 women) had a median age of 63 years (range, 37 to 76 years). Thirty-six patients had adenocarcinoma (pancreatic head, 34; distal bile duct, 1; ampulla, 1), 4 patients had nonfunctioning islet cell tumors of the pancreatic head, and 1 patient had small cell carcinoma of the pancreatic head.

Operation characteristics are listed in Table 1. Pancreaticoduodenectomy was performed in 39 patients and total pancreatectomy in 2 patients; segmental resection of the SMV–PV confluence was required in 2 patients. No patient failed to receive EB-IORT because of operative complications during the time period of this study.

The median cone diameter (treatment field) was 7 cm (range, 5 to 10 cm). Four patients had a grossly positive retroperitoneal margin and received 20 Gy of EB-IORT; 12 patients had an unsuspected microscopic focus of carcinoma within 2 mm of the retroperitoneal resection margin on frozen section analysis and received 15 Gy; and the remaining 25 patients had a negative retroperitoneal margin and received 10 Gy. The additional time required to deliver EB-IORT, from completion of tumor resection to initiation of reconstruction, averaged 50 minutes.

Operative Mortality and Morbidity

Perioperative complications are listed in Table 2. One perioperative death resulted from a myocardial infarction on the third postoperative day. Reoperation was required in four patients: one patient required reoperation for drainage of a phlegmon caused by an anastomotic

Table 1. OPERATION CHARACTERISTICS (41 PATIENTS)

Operation Characteristic	Mean	Median	Range
Operation time (h)	9.1	9.0	6.0–15.0
Operative blood loss (mL)	1178	1000	250-3000
Perioperative transfusions (units)	1.9	2.0	0–7.0
Hospital stay (days)	23	20	9–70

Table 2. PERIOPERATIVE COMPLICATIONS (41 PATIENTS)

Complication	Total	No. of Patients with Complication: Preoperative Chemoradiation	Previous Laparotomy*	Treatment of Complication
Myocardial infarction†	1	1	1	Medical
Pancreatic leak	1	0	1	Reoperation
SMV thrombosis	1	1	1	Reoperation
Splenic infarct	1	0	1	Reoperation
Small bowel perforation	1	0	0	Reoperation
Abdominal abscess	5	3	2	Percutaneous drainage
Superficial wound infection	3	1	0	Open drainage

* Laparotomy with biopsy and/or gastric or biliary bypass performed elsewhere before referral.
† Resulted in patient death. This was the only perioperative death.

leak at the pancreaticojejunostomy site; one patient who did not undergo segmental vein resection required reoperation with vein patch angioplasty for an occluded SMV resulting from a technical error during the primary operation; one patient required reoperation for splenectomy because of splenic infarction after a failed attempt at splenic preservation during total pancreatectomy; and one patient required reoperation for a perforation of the small bowel caused by a feeding jejunostomy tube. Percutaneous catheter drainage of abdominal fluid collections was required in five patients. Amylase levels in the drainage fluid were low in all five patients, and no patient exhibited clinical signs or symptoms of a pancreatic anastomotic leak. Gram-positive cocci and enteric gram-negative rods grew from the presumed abscess collections; no unusual pathogens were isolated. All five patients recovered rapidly after percutaneous drainage. Three other patients experienced superficial wound infections that required minor bedside incision and drainage. Overall, 13 patients (32%) experienced some type of perioperative complication (Table 2). In the 24 patients treated with preoperative chemoradiation, 6 (25%) experienced a perioperative complication. Nineteen patients had undergone laparotomy before referral, and 6 (32%) of these experienced a perioperative complication.

At a median follow-up time of 8 months (range, 2 to 31 months), no patient has shown clinical signs or symptoms of mesenteric vascular thrombosis or has died of an acute unexplained abdominal catastrophe. Only one patient had portal vein thrombosis identified on follow-up computed tomography scan. This patient had extensive carcinomatosis with tumor recurrence at the level of portal vein occlusion.

DISCUSSION

Pancreaticoduodenectomy and EB-IORT can be performed with acceptable morbidity and mortality. In the four cases requiring reoperation, the cause was not related to the delivery of EB-IORT. The patient who underwent reoperation and vein patch angioplasty of the SMV and the patient who required splenectomy represented errors in surgical judgment, as these procedures should have been performed at the time of initial laparotomy. One patient underwent reoperation for repair of a small bowel perforation caused by a jejunostomy tube; the mechanism of this injury remains unclear as this type of tube has been placed intraoperatively at our institution in more than 200 patients without a similar complication. One patient experienced a delayed pancreatic leak manifested as a subfascial phlegmon 4 weeks after pancreaticoduodenectomy. This patient had extensive local disease, was operated on early in our experience, and would not currently fulfill our criteria for surgical resection. There were no other complications related to the pancreaticojejunostomy. Perioperative complications in those patients receiving preoperative chemoradiation (6 of 24 patients, 25%) and in those undergoing reoperative pancreaticoduodenectomy (6 of 19 patients, 32%) were no higher than those in the total study population (13 of 41 patients, 32%) (see Table 2).

The incidence of abdominal abscess and superficial wound infection may have been related to the time and manipulation involved in the delivery of EB-IORT. Potential violations in sterile technique during patient positioning under the linear accelerator may increase the risk of infectious complications. However, all eight of the patients with infectious complications had experienced preoperative weight loss of approximately 5% to 10%, and the three patients with superficial wound infections also had serum albumin levels of less than 3.5 mg/dL, suggesting potentially significant malnutrition. Patients who undergo major intra-abdominal surgery for malignancies are at a higher risk of complications if they are malnourished.[31] Currently, in those patients who undergo preoperative chemoradiation, we place a laparoscopic feeding jejunostomy tube at the time of initial staging to prevent treatment-related nutritional depletion.[32] All infectious complications in this study resolved rapidly with nonoperative drainage and systemic antibiotics.

The rationale for an extended Kocher maneuver is the high incidence of lymph node positivity in the posterior pancreaticoduodenal region, as initially reported by Cubilla et al.[33] and confirmed in a recent study by Kayahara et al.[34] This maneuver adds little time to the operation, incurs no additional blood loss, and is technically not difficult. The purpose of the procedure is to decrease local tumor recurrence. Although it is unlikely that therapeutic maneuvers directed at the primary tumor and regional nodal basins will have any impact on the incidence of distant metastatic disease,[8,12] improved local control in the bed of the resected pancreas and regional nodal basins may improve the quality and length of survival.[8,9,23]

The retroperitoneal margin is rarely evaluated pathologically yet represents the site at greatest risk for retained tumor cells after resection. A more extensive retroperitoneal dissection with full mobilization of the SMV–PV confluence and dissection of the proximal SMA is necessary to obtain a negative retroperitoneal margin. Perineural invasion involving the mesenteric plexus at the SMA origin, as well as tumor cell infiltration within lymphatic vessels and connective tissue, may extend beyond the confines of the palpable tumor.[35,36] A negative retroperitoneal margin combined with EB-IORT boost may decrease local recurrence and enhance survival.[14,23] In addition, clear identification of the SMA avoids the potential for iatrogenic injury. Unlike regional pancreatectomy, the surgical procedure described herein is not associated with excessive blood loss or transfusion requirements (Table 1).

Based on a previous study in which one patient experienced fatal pancreatic necrosis after EB-IORT,[23] we excluded the pancreatic remnant from the IORT field.[22] However, more than half of our patients had received preoperative chemotherapy and radiation therapy.[25] The preoperative radiation field included the primary tumor and pancreaticoduodenal, porta hepatis, and celiac axis lymph node groups with a field size of 10 to 15 cm^2. In these patients, the pancreas received 50 Gy of external-beam irradiation before surgery. Ishikawa et al. have suggested, however, that preoperative irradiation decreases the potential for pancreaticojejunal leak due to decreased pancreatic exocrine function after external-beam radiation therapy.[37] Most of our pancreaticojejunal anastomoses were performed over a small silastic stent (Dow Corning Corp., Midland, MI) in two layers using the duct-to-mucosa technique. It is clear from our data that anastomotic complications were uncommon when a standardized reconstruction was performed, even when patients received preoperative chemoradiation and EB-IORT.

The combined use of external-beam radiation therapy and EB-IORT allows delivery of a higher dose of radiation to high-risk nodal groups without damage to adjacent organs and tissues. The dose of EB-IORT we used is based on preclinical and clinical studies demonstrating the safety of 20 Gy or less.[24,38–40] The major retroperitoneal blood vessels (aorta, celiac axis, SMA, SMV, PV, and IVC) that are included in the EB-IORT field are not susceptible to radiation injury, unlike hollow viscera and solid organs, although long-term follow-up will be necessary to determine the true extent of vascular injury.[41,42]

In patients with potentially resectable pancreatic cancer, treatment failure is due to local recurrence, peritoneal seeding, and/or liver metastases. The operation we describe in conjunction with EB-IORT delivered to the bed of the resected pancreas represents a logical strategy for improving local tumor control. Assessment of its effectiveness awaits further follow-up. Currently, however, local recurrence within the EB-IORT treatment field has been suggested by computed tomography scan in 4 of 25 patients with adenocarcinoma who had negative retroperitoneal margins; the median time to recurrence has been 10 months (range, 6 to 14 months). A typical low-density lesion in proximity to the SMA origin on computed tomography scan has been interpreted as a local recurrence, regardless of clinical symptoms; histologic or cytologic confirmation of recurrent disease has not been obtained. Only one patient has had a clinically symptomatic local recurrence, manifested by ascites resulting from portal vein thrombosis and progressive carcinomatosis.

We currently combine preoperative chemoradiation therapy with surgery and EB-IORT in patients with localized, resectable adenocarcinoma of the pancreas. Previous work from our institution has demonstrated the safety of pancreaticoduodenectomy after preoperative chemoradiation therapy.[25] The data reported here, representing the largest experience to date, suggest that EB-IORT after pancreatic resection is safe, well tolerated, and a potentially effective treatment strategy against local tumor recurrence.

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