Intraoperative Electron Beam Irradiation for Patients with Unresectable Pancreatic Carcinoma

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Since 1978 we have used electron beam intraoperative radiation therapy (IORT) to deliver higher radiation doses to pancreatic tumors than are possible with external beam techniques while minimizing the dose to the surrounding normal tissues. Twenty-nine patients with localized, unresectable, pancreatic carcinoma were treated by electron beam IORT in combination with conventional external radiation therapy (XRT). The primary tumor was located in the head of the pancreas in 20 patients, in the head and body in six patients, and in the body and tail in three. Adjuvant chemotherapy was given in 23 of the 29 patients. The last 13 patients have received misonidazole (3.5 mg/M^2) just prior to IORT (20 Gy). At present 14 patients are alive and 11 are without evidence of disease from 3 to 41 months after IORT. The median survival is 16.5 months. Eight patients have failed locally in the IORT field and two others failed regionally. Twelve patients have developed distant metastases, including five who failed locally or regionally. We have seen no local recurrences in the 12 patients who have been treated with misonidazole and have completed IORT and XRT while 10 of 15 patients treated without misonidazole have recurred locally. Because of the shorter follow-up in the misonidazole group, this apparent improvement is not statistically significant. Fifteen patients (52%) have not had pain following treatment and 22 (76%) have had no upper gastrointestinal or biliary obstruction subsequent to their initial surgical bypasses and radiation treatments. Based on the good palliation generally obtained, the 16.5-month median survival, and the possible added benefit from misonidazole, we are encouraged to continue this approach.

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DESPITE ADVANCES in many areas of oncology, carcinoma of the pancreas remains a rapidly lethal disease. Because tumors are not found early, pancreatectomy is possible in only 15 to 20% of patients at presentation. An additional 20% have localized disease but are not resectable.[1] Interest in the role of radiation therapy in the management of these patients has increased over the last decade since the encouraging report from Duke University in 1973.[2] While palliation is often possible, the radiation dose required for local control of pancreatic carcinoma by conventional external beam irradiation alone or by particle beams (neutrons or helium ions) is greater than the tolerance of the surrounding normal tissues.[3] Intraoperative radiation therapy (IORT) has been devised as a method to safely deliver higher radiation doses to the pancreatic tumors than are possible with external beam techniques while minimizing the dose to the surrounding normal tissues.[4-7] The specialized IORT methods include permanent radioactive seed implantations (now mainly by Iodine-125) and the use of intraoperative beam therapy (mainly of high energy electrons). Since 1978 we have elected to give IORT to patients with unresectable carcinoma of the pancreas by electron beam rather than by Iodine-125 implantation because larger tumors can be treated, the dose delivered is more uniform, the trauma to the peripancreatic tissue is less, the radiation therapy field is broader so that the high-dose volume can include a 1- to 2-cm margin outside the gross tumor volume, and the possibility of seeding cancer from an implantation is eliminated. We now report the results of our first 29 patients with unresectable carcinoma of the pancreas who were treated by electron beam IORT in combination with conventional external beam radiation therapy (XRT) and, in most of the patients, chemotherapy in an attempt to achieve the best possible tumor control and optimal quality of life.

Materials and Methods

Patient and Tumor Characteristics

During the 5½-year period from May 1978 through November 1983, 29 patients (12 women and 17 men) with a mean age of 59 years (range, 36 to 80 years) were

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TABLE 1. *Patient Characteristics*

Symptom/Factor at Diagnosis	Number	Per cent
Patients explored with IORT planned	62	100
Patients not treated with IORT	29	47
Reasons		
Distant metastases present	22	
Local-regional disease too extensive	5	
Radical resection possible	1	
Exposure of tumor too difficult	1	
Patients with unresectable tumors treated with IORT	29	47
Symptoms		
Jaundice	18	
Pain	16	
Weight loss of more than 10 lbs	11	
Pre-existing diabetes	1	
Patients treated with IORT and resection	4	6

treated with intraoperative electron beam irradiation at the Massachusetts General Hospital (MGH) for unresectable carcinoma of the pancreas. The selection criteria for patients to be eligible for inclusion into this study were: 1) biopsy-proven adenocarcinoma of the pancreas; 2) a localized unresectable tumor capable of inclusion in the high-dose intraoperative "boost" volume; 3) no distant metastatic disease; and 4) no contraindications to a surgical exploration. During this interval, 62 patients who have undergone thorough preoperative radiographic evaluation and often peritonoscopy were explored with the intent of giving IORT. However, in 29 patients (47% of the total group) IORT was not given (Table 1). The symptoms at presentation of the 29 patients who did undergo IORT for unresectable pancreatic carcinoma are shown in Table 1.

TABLE 2. *Tumor Characteristics*

Tumor	Number	Per cent
Location		
Head	20	69
Head and body	6	21
Body and tail	3	10
Size (largest diameter)		
3.5 to 4.9 cm	9	31
5 to 5.9 cm	9	31
6 to 8 cm	11	38
Local and regional extent		
No extrapancreatic spread (except to vessels)	15	52
Extrapancreatic spread	14	48
Lymph nodes	6	21
Retroperitoneal soft tissue	6	21
Other (pylorus, common duct)	2	7
Reason for unresectability		
Vessel encasement	23	79
Extension outside pancreas	5	17
Medically unfit	1	3

The primary tumor was located in the head of the pancreas in 20 patients, in the head and body in six patients, and in the body and tail in the other three. Eleven patients presented without jaundice but with pain from extrapancreatic spread, including five patients with head of pancreas cancers and three with combined head and body cancers. Fourteen of the 29 patients had evidence of extrapancreatic spread on surgical evaluation. Six (21%) had lymph node metastases, six (21%) had direct invasion of the retroperitoneal soft tissues, one had invasion of the pylorus and one invaded extrapancreatic common duct (Table 2). The surgical criteria for unresectability were: fixation to major vessels, 23 (79%); extrapancreatic tumor extension, five (17%); and medically unfit, one (3%). In 20 of the 29 patients, the largest tumor-diameter was between 5 and 8 cm while in the remaining nine patients the largest diameter was between 3.5 and 4.9 cm (Table 2).

Electron Beam IORT Technique

As previously described,[8] the surgeon and the radiation therapist assess the extent of disease at operation and a lucite cylinder of appropriate size (6 to 9 cm in diameter) is selected to cover the primary tumor mass. The operating team then defines the dimensions and extent of the tumor. This requires taking down the gastrocolic omentum, reflecting the stomach superiorly, and performing a Kocher maneuver. The lucite cylinder limits the amount of normal tissue that is irradiated by retracting nearby radiation sensitive normal tissues (stomach, jejunum, transverse colon, liver, and usually a large portion of the duodenum) outside the cylinder and, thus, outside the region of high radiation dose that is confined to the inside of the cylinder. Portions of the common duct and the stomach that will subsequently be used for biliary and gastric anastomoses are, whenever possible, excluded from inside the treatment cylinder. However, it is usually not possible to exclude the medial wall of the first, second, or third portions of the duodenum. The energy of the electron beam is selected on the basis of the thickness of the tumor (Fig. 1). The energy has ranged from 15 to 29 MeV, corresponding to a depth for the 90% isodose line of 3.8 to 6 cm, respectively.

At the MGH, anesthetized patients are transferred with the incision temporarily closed from the third floor operating room to the linear accelerator suite. There the incision is reopened and the lucite cylinder repositioned. The cylinder is then docked into an aluminum jacket attached to the head of a Clinac 35 (Varian Corporation, Palo Alto, CA) linear accelerator. The patient, with the appropriate monitoring by the anesthesiologist, is irradiated over a 3- to 5-minute interval while breathing 100% oxygen to maximize radiation sensitivity. After completion of radiation, closure may be accomplished

in the radiation therapy suite (14 of our cases) or, if bypasses or other manuevers are still necessary, the patient is transferred back to the operating room (15 cases).

During this 5½-year interval, we were seeking to determine dose tolerance to IORT. Accordingly, we initially used a dose of 1500 cGy[1]* as the IORT "boost," which we increased to 1750 cGy and then to 2000 cGy when evidence of local recurrences developed at the lower dose levels and when the normal tissue tolerance was found to be acceptable. In 1982 we began using intravenous (I.V.) misonidazole, a drug that sensitizes hypoxic cells to radiation. In theory, hypoxic cells would be present in these large unresectable tumors as is consistently true in animal tumors. Without misonidazole, the hypoxic tumor cells would be partially protected from the IORT dose.

Carcinoma, Head of Pancreas

7 cm LUCITE CONE 23 MeV

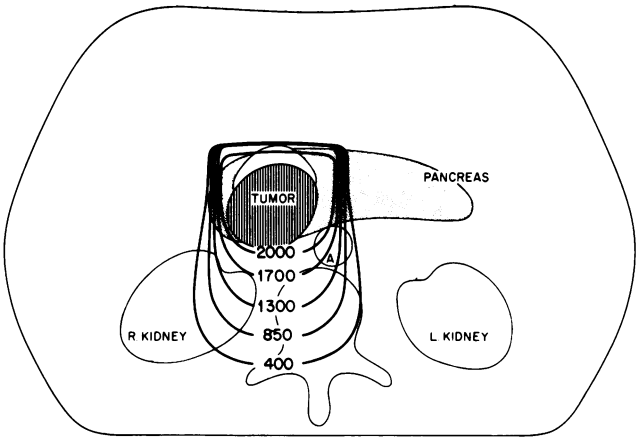

FIG. 1. Isodose curve in transverse section of electron beam IORT of 23 MeV.

External Beam Radiotherapy and Chemotherapy Techniques

Patients received 1000 to 2000 cGy of external beam irradiation (XRT) in 1 to 2 weeks to the primary tumor and regional lymph nodes 1 to 10 days prior to exploration (7 patients) or re-exploration (22 patients) for the IORT boost. After surgery, 27 of the 29 patients received an additional 3000 to 4000 cGy (total external beam dose 5000 cGy) XRT with a 4-field box technique that allowed sparing of the renal parenchyma and the spinal cord (Table 3). Chemotherapy with I.V. 5-FU (500 mg/M^2) was given on each of the first 3 days of the postoperative XRT in 20 patients. Maintenance chemotherapy (a combination of 5-FU, Adriamycin, and mitomycin-C) was administered following completion of radiation therapy to 15 patients, 11 of whom received treatment for at least 3 months (Table 3).

Statistical Methodology and Response Criteria

Life-table probabilities of survival and time to local recurrence were calculated using the method of Kaplan and Meier.[9] Survival and local recurrence distributions were compared using the one-sided log rank test (Mantel-Haenszel Procedure).[10] Prognostic variables were evaluated using the Cox proportional hazards model,[11] as well as the log rank test, with survival time as the outcome variable.

All times were measured from the initiation of radiation. This was, in the 22 patients who required a second exploration for the treatment, a median of 1.4 months after the original surgery. Patients were scored as having clinical evidence of local recurrence if they had recurrence of their pretreatment symptoms or had an increase in the primary tumor size by computed tomography or an elevated CEA in the absence of distant metastases. The presence of gastric or biliary obstruction due to tumor was based on careful review of all clinical records. No patient was lost to follow-up.

* 1 cGy = 1 rad.

Results

Patient Survival and Analysis of Disease Recurrence

At present 14 patients are alive and 11 are alive without evidence of disease from 3 to 41 months post-treatment. Of the 19 patients treated before 1983, 15 lived at least 1 year. The median overall survival is 16.5 months (Fig. 2). Eight patients have failed locally within the IORT field and two additional patients have failed regionally within the external beam XRT field. The diagnosis of local recurrence was based on histology in two, computed tomography in three, and on clinical symptomatology or physical findings in five. Twelve patients have developed

TABLE 3. *Treatment Characteristics*

Treatment	Number	Per cent
Given IORT for unresectable carcinoma	29	100
Completed all planned RT	27	93
No adjuvant CT	6	21
Maintainance CT—3 months	11	38
Misonidazole with IORT	13	45
IORT dose		
1500 cGy	5	17
1750–1800 cGy	7	24
2000 cGy	17	59
IORT on first exploration	7	24
IORT on second exploration	22	76

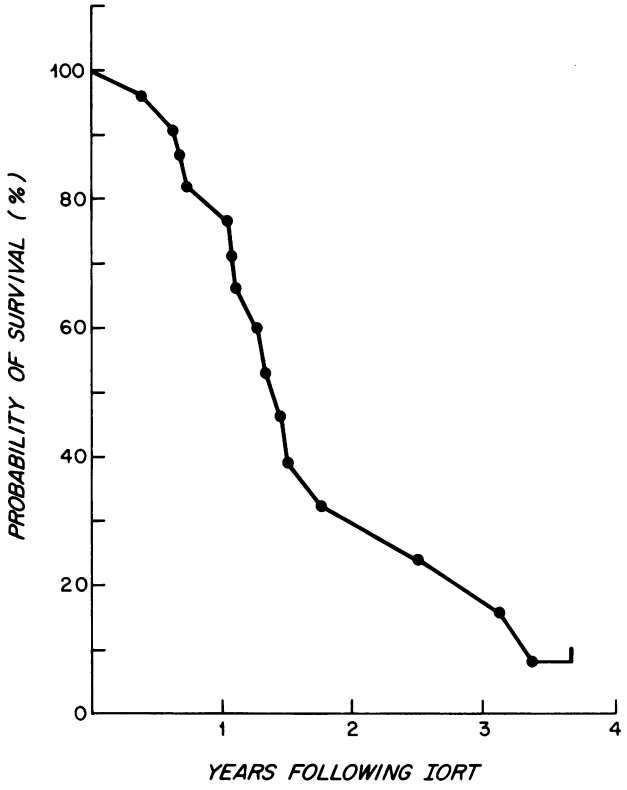

FIG. 2. Survival of 29 patients treated with electron beam IORT for unresectable carcinoma of the pancreas in combination with external beam irradiation and, in 23, chemotherapy.

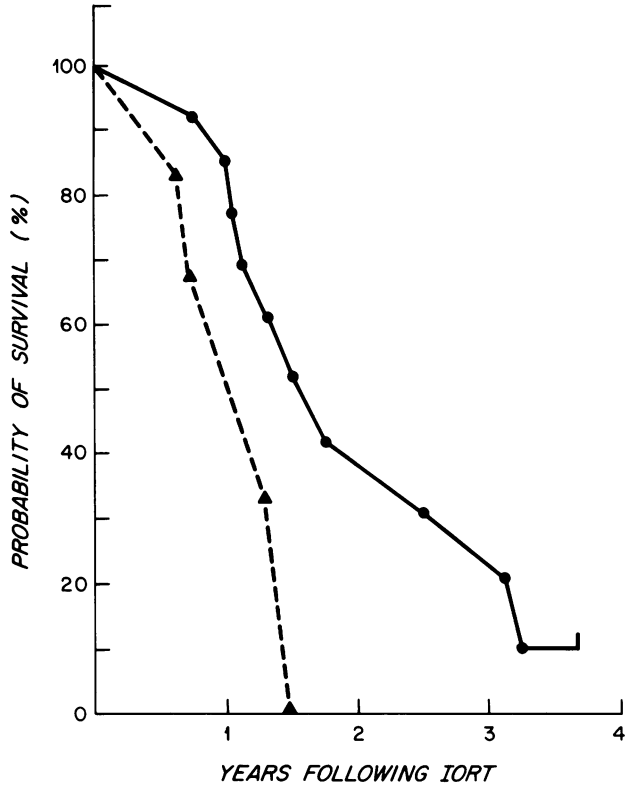

FIG. 3. Survival of the 27 patients with unresectable carcinoma of the pancreas who completed all planned therapy grouped by size of primary tumor (largest diameter). Top curve, tumors 3.5 to 5.9 cm (16 patients). Bottom curve tumors 6 to 8 cm (11 patients). The p = 0.12 (log rank test).

distant metastases. Three are alive at 5 to 11 months and nine have died, including five who had evidence of local or regional recurrence. A diagnosis of distant metastases was based on pathology in four patients, radiographic information in three patients, and on clinical grounds in five patients (evidence of diffuse peritoneal seeding).

Of the 27 patients who completed the planned radiation therapy, for example, 1500 to 2000 cGy of IORT and 5000 cGy of external beam irradiation, several factors seem to be associated with an improved result (Table 4). Both median survival and the probability of local control for 1 year were better in those patients receiving adjuvant chemotherapy than the small subgroup who did not (p = .04). Tumor size may influence both local control and survival but as yet not at the level of statistical significance (Fig. 3). We have seen no local recurrences in the 12 patients who have been treated with misonidazole and completed the planned radiation therapy, while there have been 10 local recurrences in the 15 patients completing all planned radiotherapy without using misonidazole. The short follow-up on the patients treated concomitantly with IORT and misonidazole prevents this difference from reaching statistical significance for either survival or local control (Fig. 4).

TABLE 4. *Treatment Results*

Patient Characteristic	Number	Median Survival (Mos)	Probability of Local Control at 12 Mos
			Per cent
All patients	29	16.5	64
Completing planned RT	27	17	69
No adjuvant CT	4	8	38
Combined RT and CT	23	17	76
Tumor diameter 3.5–5.9 cm	16	19	78
Tumor diameter 6–8 cm	11	11	53
IORT with misonidazole	12	Undefined	100
IORT without misonidazole	15	17	61

Treatment Complications

There have been neither anesthetic complications nor perioperative wound infections in these patients. Median postoperative hospital stay was 12 days (range 6 to 69 days). There were no perioperative deaths. In the 13 patients receiving I.V. misonidazole (3.5 gm/M^2 over 30

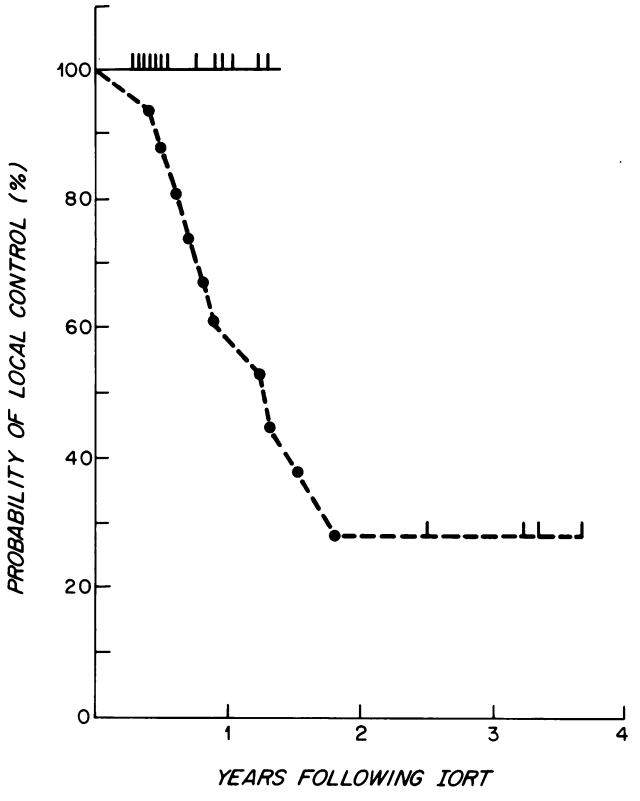

FIG. 4. The local control rate of the 29 patients with unresectable carcinoma of the pancreas treated with IORT. Top curve, misonidazole plus IORT (13 patients). Bottom curve IORT alone (16 patients). The verticle bars indicate the interval of follow-up for patients who are controlled locally.

minutes usually in 250 ml), there were no untoward reactions.

There were three significant postoperative complications. The first was a suture line leak of the gastric antrum in the immediate postoperative period. Exposure of the tumor for IORT required division of the stomach. The antrum was closed with a GIA stapler. The complication presented too early to have been irradiation-induced. A second patient developed, in her second postoperative week, a pancreatic abscess from *Candida* that was controlled with systemic antifungal therapy. Neither of these two patients were able to complete their planned postoperative course of external beam irradiation. The third patient had delayed gastric emptying following the IORT and gastrojejeunostomy. This took 5 weeks to resolve.

The late reactions or injuries that may be related to the high radiation dose are listed in Table 5. Four patients sustained pyloric or duodenal injury that was in the IORT field. One resulted in obstruction. This was corrected by a gastroenterostomy that had not been done at the time of the original IORT. Three patients had bleeding from the duodenum or pylorus. One was controlled with Pitressin and one occurred just prior to the patient succumbing from hepatic failure from extensive liver metastases. The remaining patient with a bleeding site in the IORT field and two of four additional patients with bleeding sites in the external beam field responded to antacid therapy.

TABLE 5. *Treatment Complications*

Reaction	Number	Per cent
Perioperative complications		
Anesthetic	0	0
Operative deaths	0	0
Major; from surgery and/or RT	3	10
Late reactions or injury		
Upper GI bleeding	7	24
Gastric outlet obstruction	1	3
Biliary obstruction	2	7
Superior mesenteric artery occlusion	1	3
Exocrine insufficiency	10	34
New diabetes	1	3

Three patients have developed retroperitoneal radiation fibrosis with secondary obstructions. Two patients had occlusion of the common duct with jaundice which on surgical exploration proved not to be due to recurrent tumor and was corrected. A third patient developed upper small bowel necrosis. Autopsy revealed: 1) fibrosis throughout the region of the pancreas; 2) generalized severe arthrosclerosis; and 3) nearly complete occlusion of the superior mesenteric artery from intimal proliferation. Finally, ten patients have required oral enzymes for mild to moderate symptoms of pancreatic exocrine insufficiency.

TABLE 6. *Palliative Benefits*

Symptom	Treatment Result	Number	Per cent
Pain on presentation (16 patients	Complete relief, maintained	8	50
	Complete relief but recurred	4	
	Partial relief only	4	
No pain on presentation (13 patients)	Never developed pain	7	54
	Developed pain with recurrence	4	
	Developed pain with complications	2	
No pain following treatment		15	52
Late upper GI obstruction	Local tumor recurrence	2	
	Radiation fibrosis	1	
Late biliary obstruction	Local tumor recurrence	1	
	Radiation fibrosis	2	
Late upper GI biliary obstruction	Local tumor recurrence	1	
No obstruction following treatment		22	76

Palliative Benefits

Sixteen of the 29 patients had pain prior to treatment. Twelve of the 16 patients were relieved of their pain following radiation and pain was significantly reduced in the other four (Table 6). Of the ten patients who had a local or regional regrowth of tumor, eight were symptomatic with pain and four developed biliary and/or upper gastrointestinal (GI) obstruction due to tumor regrowth. Thus, of the 29 patients with unresectable pancreatic carcinoma, 15 (52%) never developed pain following treatment and 22 (76%) had no upper GI or biliary obstruction subsequent to their initial surgical bypasses and radiation treatments. In 16 patients with survival of 6 to 41 months, each patient has on average "felt well" 70% of the time (range 36 to 92%; median 71% of the time). Thus, even though all patients had unresectable cancers, the overall quality of survival was good and patients were relatively free of recurrent upper abdominal difficulties.

Discussion

A full analysis of our experience with combined IORT and external beam radiation therapy and chemotherapy for patients with unresectable pancreatic carcinoma is not yet possible. This is due to low patient numbers and short follow-up of many patients and by the escalating dose levels of IORT used in this pilot study. The median survival of 16.5 months is longer than that in other series using radiation therapy and longer than many series where radical resection was employed in a more favorable subset of patients.[1,12-14] However, our series does not as yet have any long-term (5-year) survivors as are reported in about 10% of patients treated with radical resection.

Eight of our 29 patients have recurred locally in the IORT-treated field and two others have failed regionally in the external beam field. While this is a disappointingly high recurrence rate, it does compare favorably with that seen with external beam radiation alone, in which 60 to 70% of the patients have been symptomatic with recurrence.[15,16] We are encouraged that since combining misonidazole with the IORT we have not seen a local recurrence (Fig. 4), although follow-up is still short. The improved survival in patients receiving chemotherapy as well as radiation (Table 4) may result more from patient selection than from cytotoxic effect.

Many patients with unresectable pancreatic carcinoma (as well as those undergoing resection) will fail outside the primary treatment area even if that area is sterilized. Thus it is unfortunately necessary to approach patients having pancreatic carcinoma with palliation as a primary objective, and one must recommend with caution any radical local treatment that may be associated with substantial long-term morbidity.[17] We are concerned that three patients developed common duct or vascular obstruction due to late radiation fibrosis. However, based on our relatively long median survival time, the good palliation generally obtained, and a possible added benefit from misonidazole, we are encouraged to continue this approach.

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