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PANCREATIC CARCINOMA: RESULTS WITH  
FAST NEUTRON THERAPY

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## PANCREATIC CARCINOMA: RESULTS WITH FAST NEUTRON THERAPY

Incidence of pancreatic carcinoma has tripled over the last 40 years, an alarming increase.<sup>1</sup> It accounts for 20,000 deaths per year, ranking as the fourth leading cause of death among cancer patients exceeded only by lung, colon and prostate cancers. Cancer statistics, based upon NCI Surveillance Epidemiology and End Results (SEER) Program (1973 - 1976) predict an estimated incidence of 3% of all cancers, but 5.5% of all cancer deaths. These figures reflect the highly lethal nature of the disease, as is documented by an extremely poor 5 year survival rate, viz., 1 to 2%, one of the lowest of all cancers.<sup>2</sup>

The reasons for its increasing incidence remain obscure, but for poor survival may be twofold. Survival rates remain low due to problems relating to early diagnosis as well as difficulty in treatment. At the time of presentation a very small percentage of the patients can have the benefit of a curative resection. Only 15% of the patients have disease confined to the pancreas

alone (Stage I), 20% have evidence of spread to regional lymph nodes (Stage II) and 65% have evidence of liver metastasis (Stage III).

#### Materials and Methods.

At Fermi National Accelerator Laboratory, 50 patients have been treated as a part of Phase I and II study since patient accrual began in 1976. Of these, 38 patients have a minimum follow-up of 11 months. Six patients with evidence of distant metastases at the time of treatment were excluded from this study. One patient was originally diagnosed to have an undifferentiated carcinoma, but at autopsy was proven to be Reticulum cell sarcoma and was therefore not included in this analysis. Thirty-one patients are the subject of this presentation.

Patients were followed at regular intervals - the initial visit being one month after finishing the treatments and then at three monthly intervals. Follow-up studies included CT scans, UGI series, liver function tests and liver scans besides a complete physical examination.

#### Patient Population.

Age: Patients' ages ranged from 45 years to 77 years with a median of 60 years.

Symptoms: Abdominal discomfort and pain in varying degrees were the most common presenting symptoms, followed by weight loss and jaundice. Nausea and vomiting occurred less frequently.

Surgery: All of these patients underwent exploratory laparotomy to provide tissue for histopathological diagnosis and a biliary by-pass to relieve or prevent obstruction. These were performed at referring institutions.

Cholecystojejunostomy was carried out in most patients, except for the following:

2 patients underwent incomplete resections,

1 patient had choledochoduodenostomy,

1 patient did not undergo any by-pass.

Pathology: According to the pathological classification suggested by Cubilla and Fitzgerald<sup>3</sup> all patients had typical adenocarcinoma of the pancreas except three. One had mucinous adenocarcinoma, 1 had ampullary carcinoma and 1 had possibly an APUD tumor.

Site and Extent: Tumor originated in the head of the pancreas in 10 patients, in the body and tail in 9 patients and involved the whole of the pancreas in 3 patients. In the remaining

it was unknown. Table II depicts the number of patients according to their site of involvement. Primary tumors were large, up to 18 x 12 cm in size, and regional lymph node involvement predominated. Portal vein obstruction, superior mesenteric and mesocolic lymph node involvement and retroperitoneal fixity were commonly encountered features.

#### Pre-Treatment Work-up.

CBC, SMA&B, x-ray chest, upper GI series and cholangiogram were obtained pre-operatively. Occasionally pancreatic scans, sonograms of the pancreatic region, ERCP and arteriography were also obtained. Intra venous pyelograms in erect posture and computerized axial scans of the abdomen were obtained prior to treatment in all patients since October, 1978.

#### Technique.

Patients were treated on out-patient basis. Treatment was carried out 2 to 3 times per week for a total of 6 to 7 weeks. Due to the horizontal nature of the emerging beam, patients were treated in the erect position. An equivalency factor (RBE) of 3 is estimated for the re-

latively high energy neutron beam at Fermilab generated by 66 MeV protons on a thin beryllium target.<sup>4</sup>

A target volume was defined with 2 cm margins around gross tumor, usually between 1000 and 1700 cm<sup>3</sup>. This was adequately covered by one anterior port and 2 wedged lateral portals resulting in a satisfactory dose distribution as shown in Fig. 1. Vital structures like the kidneys and the spinal cord created limitations and therefore appropriate adjustments were made. Generally a dose of 19.5 Gy was delivered in 13 fractions over 6 to 7 weeks. Only 3 patients received lesser doses, i.e., one received 16.5 Gy, and two received 17.5 Gy. One patient received 45 Gy with photons and 8.0 Gy with neutrons.

### Results.

**Tolerance:** Treatment was well tolerated by most patients. No hematologic toxicity was observed in patients who had complete blood counts during and after treatment. Minimal symptoms attributable to GI irritation were encountered.

Pain relief came within a few days of initiation of treatment. Of 15 patients with severe

pain at the time treatments were initiated, 9 had significant relief, 5 had little or no relief from pain. Deterioration of condition occurred in one patient due to rapid progression of disease.

Median survival of these 31 patients is 9 months, ranging from 3 to more than 28 months. To-date 6 patients are alive at 28, 15, 14, 14, 21 and 11 months post-date of diagnosis. The first 3 have no evidence of disease on clinical and radiographic grounds, the fourth had a laparotomy for prepyloric obstruction due to edema and was found to be free of disease. The remaining 2 are alive with evidence of disease both within and outside the treated areas. The two year survival rate could be as high as 26%, though there is considerable uncertainty in this figure at the present stage of follow-up. Fig. II and III depict survival times from date of diagnosis. Fig. IV reflects actuarial survival of these patients.<sup>5</sup>

Inability to control the continued growth of the primary tumor in the treatment volume was the prime reason for failure. Follow-up CT scans in 8 patients, laparotomy in 2 and autopsy in 4 patients confirmed progression of disease. Besides failure in the primary site, liver was the most common site of metastases.

Complications: Eleven patients experienced 12 severe side effects of which 2 were fatal. These occurred 3 to 9 months after completion of therapy. One patient developed gastric atony 3 months after treatment. This resolved and the patient then developed a duodenal ulcer for which he had vagotomy and gastrojejunostomy. Only 1 more patient required surgery for gastric edema, the remaining resolved with conservative management. Diabetes mellitus did not occur in any of the patients as a result of treatment.

As failure of local control remained the major problem and the number of significant side effects was not excessive, an increase in dose was thought to be justified. Henceforth, patients have been treated up to a dose of 22.5 Gy in 7.5 weeks.

### Discussion.

As very few patients undergo radical extirpative procedure, be it Whipple's, a total pancreatectomy alone, or with regional lymphadenectomy, many radiation centers have been treating localized pancreatic cancer with photons. In earlier years radiotherapy was considered to be

of palliative value only in pancreatic carcinoma. The reasons may be twofold: firstly, the deep location of this organ and its proximity to vital, but dose limiting anatomic structures such as the small intestine, kidneys, spinal cord and the liver made it impossible to treat it with ortho-voltage equipment; secondly, adenocarcinoma was generally regarded as a "relatively radio-resistant" pathological subtype.

Before the late 1950s, there is a paucity of information regarding treatment of pancreatic cancer with radiation. There were only sporadic reports consisting of few patients treated with different doses and varying techniques, thus making it impossible to judge the value of radiotherapy. Whenever doses less than 50 Gy were used, the degree of palliation obtained was insignificant.<sup>6,7</sup> In 1973, Haslam, Cavanaugh and Stroup reported on 29 patients that were treated with a double split course technique using opposed ports with Co<sup>60</sup> teletherapy, delivering doses as high as 67.0 Gy.<sup>8</sup> Median survival of this group was 7.5 months.

Dobelbower has described precision high-dose (PHD) radiotherapy for unresectable adenocarcinoma of pancreas.<sup>9</sup>

Doses of the magnitude of 60 to 70 Gy are delivered over 7 to 9 weeks. "Mixed" beam therapy with 45 MeV photons and 15 to 35 MeV electrons is utilized in slender patients. Thirty-two patients treated with the PHD technique have a "mean" survival time of 12 months. Komacki, Wilson and Cox have reported similar results with a median survival of 7.0 months.<sup>10</sup>

Treatment with heavy ions such as helium have been used for pancreatic carcinoma at Berkeley and Quivey, et al, reported 8 patients to be alive and well (7 to 39 months) out of 30 that were treated.<sup>11</sup>

### Conclusions.

It is now obvious that radiotherapy has more to offer than just palliation. Also the benefits derived from it are dose-dependent. The above results and our beliefs have enabled us to go a step further in clinical research for pancreatic carcinoma. A nationwide randomized trial has been launched on the basis provided by this preliminary data. The effectiveness of high energy neutron beams alone or in combination with low LET therapy in local control, palliation of symptoms and duration of response will be evaluated along with survival rates. Also, it will determine the time of onset evolution and severity of radiation injury to organs included in the treatment portal.

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TABLE I

Tumors Categorized Based on Histopathology.

Pathology	No. of Patients
Adenocarcinoma	28
Mucinous adeno- carcinoma	1
Ampullary	1
APUD	1

TABLE II

Site and Extent of Tumor

Site	No. of Patients
Head	10
Body and tail	9
Whole	3
Unknown	9

TABLE III

Complications

Complications	No.	End result
Duodenal ulcer	3	1 - surgically corrected, 2 - conservative.
GI hemorrhage	2	2 - fatal.
Gastric atony	2	1 - resolved, 1 - persistent.
Gastric edema and obstruction	1	1 - surgically corrected.
Pancreatic insufficiency	4	4 - replacement enzymes.
Diabetes mellitus	0	

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