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TREATMENT OF PROBABLE SUBCLINICAL LIVER METASTASES AND GROSS PANCREATIC CARCINOMA WITH HEPATIC ARTERY 5-FLUOROURACIL INFUSION AND RADIATION THERAPY

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Abstract

Since subclinical hepatic metastases are frequently present at time of diagnosis of pancreatic carcinoma, any meaningful effort to improve survival must include 'prophylactic' liver therapy in addition to treatment of the pancreatic primary. We report the results of a prospective, unrandomized clinical trial of a 2-week liver and pancreas infusion (by hepatic artery) of 5-fluorouracil (5-FU) and pancreatic irradiation to 50–60 Gy, combined with prophylactic irradiation of the liver with approximately 20 Gy. Of 21 evaluable patients, 17 completed therapy without excessive toxicity and had a median survival of 50 weeks. Contrary to historical controls, the liver in our series was rarely the first site of failure (6%), suggesting that the combination of hepatic artery 5-fluorouracil and 20 Gy liver radiation may suppress subclinical (microscopic) liver metastases without significant hepato-toxicity. When radiation doses to the pancreas were increased above 50 Gy there was improvement in primary tumor control, although failure in the pancreatic bed remained the most common site of failure. Future clinical investigation of this form of combined therapy for eradication of micro-metastasis in the liver, combined with more aggressive local pancreatic therapy, would seem appropriate.

Key words: Pancreas, adenocarcinoma, subclinical liver metastases, hepatic artery 5-FU, radiotherapy.

Cancer of the pancreas first described by Bigsby in 1835 (3) remains one of the most lethal of all malignancies with more than a 99% fatality rate (4).

The incidence of pancreatic cancer in the United States is increasing. The more than 25000 cases recorded in 1985 represent the second most common gastrointestinal tumor, the seventh most common malignancy and the fifth most common cause of cancer death (1).

Only 8% of lesions are localized sufficiently to permit radical resection (14) and the 5-year survival rate of these patients is less than 4% (21). For the unresectable lesions, median survival without treatment is 3–4 months (18). Early nonsurgical approaches included both external beam irradiation as well as implantation techniques (6, 10), but results were poor probably due to the low doses (35–40 Gy) and, as we have previously reported, inadequate tumor localization procedures (22).

More recent efforts employing more than 40 Gy photon dose, fast neutrons, and intra-operative radiation (19) seem to have resulted in a doubling of the median survival to 6–8 months (7, 8). Higher doses of 160–200 Gy with interstitial implants (11) into the pancreatic tumor bed unfortunately have not improved survival. Liver and other loco-regional failures too frequently are the cause of death even with local control of the primary pancreatic mass. Single agent chemotherapy has resulted in a 6–27% objective response rate and multi-agent chemotherapy in 13–43% (5, 11) but the median survival is only 4–6 months. Combined intravenous 5-FU and radiation therapy (16, 17) to the pancreatic bed has not markedly improved survival. These studies clearly indicate that surgery and/or high dose radiation therapy to the pancreatic bed alone does not significantly improve survival, and some effective form of prophylactic treatment of subclinical liver metastases is needed. Achieving an effective therapy for eradicating subclinical liver metastases is not a trivial problem as the 50 Gy/5 weeks of whole liver radiation alone probably required for 90% control of subclinical disease is not possible due to lethal radiation hepatitis (9, 12). Our previous extensive experience with both hepatic artery 5-FU and liver radiation prompted us

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to design a protocol to combine hepatic artery 5-FU and x-ray therapy as a therapy which would not damage the liver and yet offer control of the almost certain hepatic micrometastases.

Material and Methods

Therapy. This pilot study was designed to evaluate the toxicity and effectiveness of combined radiation therapy and hepatic artery 5-FU infusion for biopsy-proven, unresectable, adenocarcinoma of the pancreas.

Exclusion criteria included tumor extending beyond a 20×20 cm radiation field, distant metastases, including hepatic angiographic evidence of metastases, ascites and previous chemotherapy or radiotherapy as well as ECOG performance status less than 3. Regional node involvement was not considered as distant. Informed consent was required of all patients.

The majority of patients underwent exploratory laparotomy and some form of surgical by-pass. Tumor debulking was not attempted in any patient. Examinations with regard to metastatic spread included chest radiogram, liver scans and/or liver function tests, CEA, selective hepatic arteriography, and CT scans, generally including intra-arterial contrast enhancement, as well as ultrasound evaluation in some patients. Thorough and complete (22–24, 26) evaluation and staging of the liver for gross metastases from pancreatic cancer, was done by hepatic angiography and often intra-arterially contrast enhanced CT, prior to the initiation of therapy so the question of suppression of subclinical hepatic disease by our therapy could be evaluated.

The treatment regimen consisted of a 2-week continuous selective hepatic artery infusion of 5-FU (15 mg/kg/day), utilizing the percutaneous transbrachial artery technique of catheter insertion and placement (24, 26). Common hepatic artery infusion, proximal to the gastroduodenal artery was used for tumor arising in the head of the pancreas, while splenic artery and proper or common hepatic artery catheters may be used for tumor in the body or tail.

Fig. 1 illustrates a hepatic artery angiogram and demonstrates the usefulness of this study to delineate the pancreas and tumor boundary for radiation portal definition, and to rule out clinical liver metastases.

Angiography and fluoroscopy with the injection of radio-opaque contrast assured that the 5-FU infusion was directed to the liver and pancreas. For quality control of the 5-FU infusion, the infusion catheter position was checked fluoroscopically at least twice a week. These studies gave us useful appreciation of tumor boundaries. Our development and use of transbrachial artery placement of these catheters, we believe, is a major breakthrough in the quality control of continuous intra-arterial chemotherapy and is preferred over the surgical placement, since it allows for outpatient catheterization and importantly for relatively simple readjustment of the catheter should catheter position change during the 2-week infusion period.

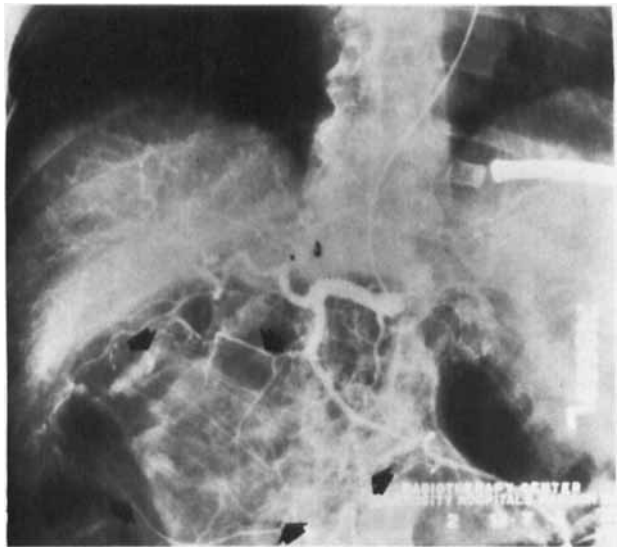

Fig. 1. Early phase hepatic artery angiogram, demonstrating normal liver and massive head of pancreas carcinoma (arrows).

Two weeks following the completion of infusion, patients were re-evaluated for disease progression, and radiotherapy was initiated. This consisted of a maximum dose of 20 Gy (1.5 Gy per fraction) to the liver, pancreas and parapancreatic and celiac nodes, using 10 MV photons. Opposed anterior and posterior fields were generally used. After a further two-week break and repeat CT evaluation for disease progression, the entire pancreas was treated (1.7 Gy per fraction) to a total dose of approximately 40 Gy. Rotational and/or lateral tumor boost fields then brought the total dose to the gross tumor-bearing region to 50–60 Gy. Either 10 MV or 4 MV x-rays or cobalt-60 were used for the boost fields.

Six weeks following completion of radiation therapy, repeat liver scans were generally obtained and patients without evidence of progression were often given systemic 5-FU at 15 mg/kg/wk. Patients were followed until death with serial liver scans, abdominal CT scans, ultrasound, chest radiograms, serum chemistry, CBC and CEA levels as indicated.

Patients. A total of 27 patients were entered on the protocol from May 1977 to May 1982. Table 1 illustrates the patient characteristics.

All patients were evaluated for 8 symptoms, analyzed in Table 2. Abdominal and/or back pain, weight loss and jaundice were the most common symptoms, present in about two thirds of patients. An abdominal mass was very uncommon, present in only 3 patients.

The tumor characteristics are presented in Table 3. The American Joint Committee on Cancer (AJCC) staging system was employed. Five patients had T1 disease while 21

Table 1

Patient characteristics

	Total patients entered on protocol	Patients who completed therapy
Total No.	27	17
Male/female	14/13	10/7
Age range	25–73	25–73
Median age	60	59
Performance status		
0	0	0
1	5	4
2	19	12
3	3	1
4	0	0

Table 2

Presenting symptoms

	Total patients entered on protocol		Patients who completed protocol	
	No.	(%)	No.	(%)
Abdominal/back pain	19	(70)	9	(53)
Weight loss	19	(70)	6	(35)
Jaundice	17	(63)	12	(70)
Anorexia	13	(48)	11	(65)
Nausea/vomiting	12	(44)	13	(76)
Pruritus	5	(19)	3	(18)
Asthenia/weakness	5	(19)	2	(12)
Abdominal mass	3	(11)	1	(6)

Table 3

Tumor characteristics (all adenocarcinoma)

	Total patients on protocol	Patients who completed therapy
T1	5	4
T2	0	0
T3	21	13
N0	12	8
N1	14	9
Grade 1	5	5
Grade 2	10	7
Grade 3–4	4	2
Grade not analyzed	8	3

were T3. One patient was not laparotomized and hence staging data were not available. Fourteen patients had positive regional lymph nodes and 12 were NO. Tumor grade was inadequately defined in 8 patients. (One patient was diagnosed by needle biopsy and the grade was therefore not available.)

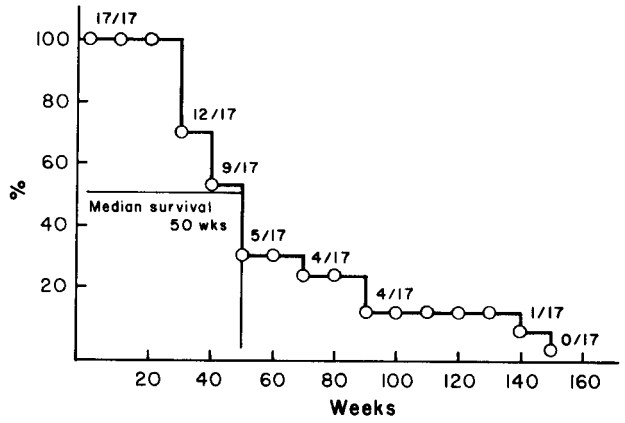

Fig. 2. Survival curve of the 17 patients who were able to complete the protocol irradiation. Median survival 50 weeks.

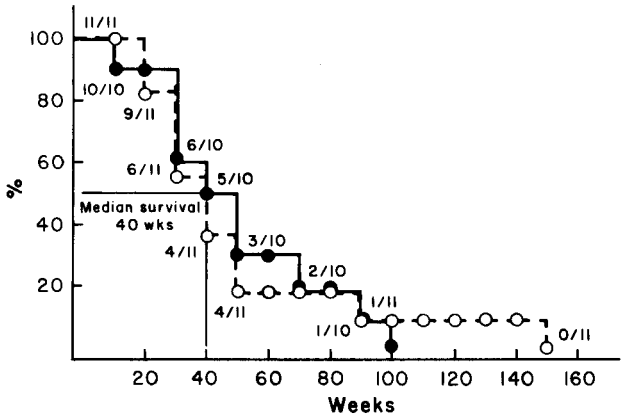

Fig. 3. Survival curves for node negative and node positive groups. Median survival 40 weeks in both groups. Node positive (n=10) ●—●. Node negative (n=11) ○---○.

Tumor location analysis revealed that the head was involved in the vast majority of patients (88%) while the tail was the most infrequently involved region (12%). The body was involved in 24% of patients.

Results

Survival. Six of the 27 patients should not have been entered on the protocol—2 because of problems with the histologic diagnosis, i.e. one had no histologic diagnosis of cancer and one had a diagnosis of adenocarcinoma of the stomach. There were also 4 who on retrospective review had distant metastases prior to commencing therapy. For these reasons we will report the survival of the 27 patients entered, as well as that of the 21 who were actually eligible for the protocol. The median survival of the total 27 patients entered on the protocol was 29 weeks; the median survival of the 21 patients who were eligible for the protocol was 40 weeks. Of these 21 patients, 4 were unable to complete the first phase of their

treatment (3 out of 4 completed the initial infusion, but received only a small fraction of the planned radiation). The survival curve for the 17 patients who completed the initial intra-arterial 5-FU and the radiation therapy is presented in Fig. 2. Median survival for this group was 50 weeks. Tables 1, 2, and 3 demonstrate no significant difference in patient characteristics, symptoms, or tumor characteristics between those who completed radiation therapy (n=17) and the total group. In general we entered patients with advanced tumors, often accepting patients who were turned down by other protocols. Fig. 3 analyzes the survival of node positive versus node negative patients in those completing therapy—i.e., both subsets of patients had a median survival of 40 weeks.

Toxicity. One patient developed multiple subdiaphragmatic and intrahepatic abscesses secondary to his primary surgery and died as a result of this. Another patient developed large bowel obstruction approximately 9 months after completion of therapy and at surgery was found to be free of tumor, but had much fibrosis around the inferior mesenteric artery, and devitalized large bowel was responsible for the patient's demise.

One patient required embolectomy from a catheter related embolus.

5-FU-related GI toxicity occurred in 5 patients. One required celiac nerve block for pain and another developed a severe chronic gastric ulcer, requiring surgery. 5-fluorouracil related transient neutropenia resulting in discontinuation or interruption of chemotherapy occurred in 3 patients.

Two patients experienced myelosuppression requiring interruption of therapy while undergoing radiation therapy.

Failure patterns. The 17 patients who completed radiation therapy were analyzed for failure patterns. The local tumor bed was the first site of failure in 12 patients (70%). The liver was the first site of failure in only one patient (6%). Two patients presented with metastatic supraclavicular nodes as the first clinical site of failure. One patient died of pneumonia unrelated to therapy and another from fibrosis of the inferior mesenteric artery.

The mean time to disease progression in this subgroup of 17 patients who completed therapy was 41 weeks. The mean time to death following disease progression was 13 weeks.

Discussion

The patient and tumor characteristics in this study are similar to those generally reported in the literature. The median survival for the entire group of 27 patients was 29 weeks, but the median survival of the 21 patients who were actually eligible for the protocol was 40 weeks and is longer than the conventionally reported median survival of 20 to 32 weeks with radiotherapy alone (8). While this compares well with other series reporting results of combined chemoradiotherapy, our subgroup of 17 patients who completed therapy had a median survival of 50 weeks and in this small series we did not obtain a survival difference between patients with and without positive nodes.

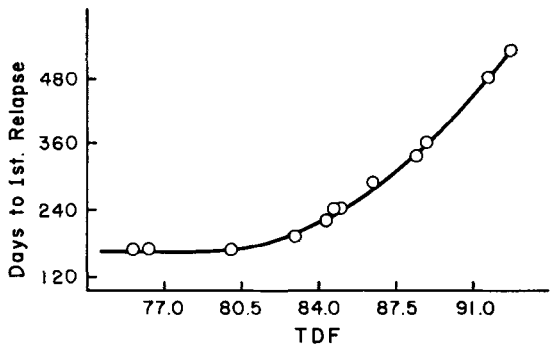

Fig. 4. Days to first relapse of tumor, as a function of TDF.

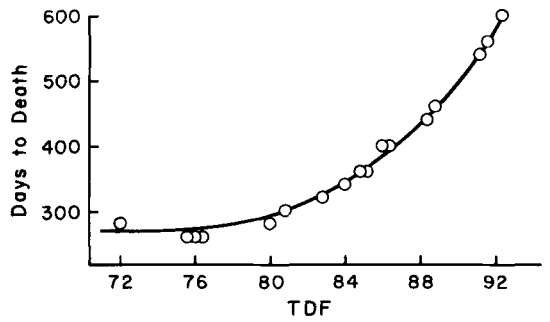

Fig. 5. Days to death, as a function of TDF. (Note that both first relapse and death endpoints significantly increase after TDF values exceed 80.)

The Mayo Clinic reported a randomized controlled double-blind study in 1968 comparing radiation therapy alone (35.00–37.50 Gy) vs. radiation therapy plus intravenous 5-FU (15 mg/kg as a single dose) once daily during the first 3 days of radiation therapy (16). The survival rate of these 2 groups was 27 and 44 weeks respectively. An ECOG study employing systemic 5-FU and 40 Gy external beam therapy reported median survival of 35 weeks (17). Previous studies report the liver as being a common first site of failure (24–38%) (2, 15, 17) but this occurred in only one of the 17 patients (6%) in our study who completed the protocol. This suggests that hepatic artery 5-FU and approximately 20 Gy radiotherapy to the liver may suppress and/or eradicate hepatic micro-metastasis and that our form of prophylactic liver treatment regimen may have a meaningful investigative role also in the treatment of colon cancer and other malignancies where death from liver metastases is also common.

The local pancreatic tumor bed as a primary failure site remains a problem, with a 70% failure rate in this study, suggesting the need for more aggressive local therapy to gross pancreatic cancer. Fig. 4 analyzes first relapse with

the total tumor dose expressed as a Time Dose Fractionation (TDF) value (20), using the least squares fit method. An obvious dose–response relationship is elicited, further suggesting that more intensive external beam x-ray therapy might result in better local control. A break point is apparent around a TDF value of 84, which roughly equates to 50 Gy in fraction sizes of 2 Gy each. A similar dose–response relationship is noted when death is used as the end-point (Fig. 5).

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