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Evaluation of Neutron Irradiation of Pancreatic Cancer

Results of a Randomized Radiation Therapy Oncology Group Clinical Trial

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Between 1980–84, the Radiation Therapy Oncology Group conducted a trial in patients with untreated, unresectable localized carcinomas of the pancreas. Patients were randomly chosen to receive either 6,400 cGy with photons, the equivalent dose with a combination of photons and neutrons (mixed-beam irradiation), or neutrons alone. A total of 49 cases were evaluable, of which 23 were treated with photons, 11 with mixed-beam therapy, and 15 with neutrons alone. The median survival time was 5.6 months with neutrons, 7.8 months with mixed-beam radiation, and 8.3 months with photons. The median local control time was 6.7 months with neutrons, 6.5 months with mixed-beam radiation, and 2.6 months with photons. These differences are not statistically significant. Evidence of moderate-to-life-threatening gastrointestinal or hepatic injury was present in three patients treated with neutrons and one patient treated with photons. The causes of this apparent difference are discussed. This study demonstrates there is no evidence to suggest that neutron irradiation, either alone or in combination with photon irradiation, produces better local control or survival rates than photon irradiation.

Key Words: Mixed-beam radiation—Neutron therapy—Pancreatic cancer—Photon therapy.

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Carcinoma of the pancreas annually accounts for over 24,000 deaths per year in the United States, where it is the fifth leading cause of cancer deaths (1). Only about 10–15% of patients are candidates for radical excision (2), and even among these patients, the 5-year crude survival rate is 15%, with local recurrences in up to 50% (3). Overall, the prognosis is poor, with only 3–5% surviving 5 years (1).

For the case that is medically or technically inoperable, radiation can palliate the local symptoms of advanced disease with relatively low doses of 3,000–4,000 cGy (4). With higher doses of 5,000–6,500 cGy (with or without chemotherapy), the symptom-free interval is extended (5), and the median survival time is typically 7–13 months (1,5–8). At the time of death, locally persistent disease is frequently seen (9,10). Thus, improvement in the local control rate should improve the overall survival rate in patients with this disease.

As an alternative to increasing the physical dose, high linear energy transfer (LET) radiation attempts to deliver a biologically more effective dose and thus improve the therapeutic ratio. The potential advantage of neutron therapy is a reflection of the biological consequences of high LET in tissue (11). The dense ionization produced by neutrons leads to more effective killing of cells protected by virtue of hypoxia. The oxygen enhancement ratio (OER) with neutrons is approximately 1.6, compared to an OER of 2.5–3.0 with high-energy photons. The repair of both sublethal and potentially lethal damage is diminished with high LET radiation as compared to photon radiation. Finally, there is less variation in radiation sensitivity as a function of cell cycle position with neutrons. In clinical practice, these potential advantages of neutron therapy have been demonstrated in the treatment of adenocarcinomas of the prostate (12,13) and salivary gland (14).

This study (Radiation Therapy Oncology Group, or RTOG, 79-21) was designed to determine whether neutron radiation alone or combined with conventional photon radiation (mixed-beam radiation) was superior to conventional photon irradiation in the treatment of locally advanced pancreatic adenocarcinomas.

MATERIALS AND METHODS

Forty-nine patients were entered in this study between February 1980 and October 1984. Mandatory prerandomization evaluation included a complete history and physical examination, laparotomy with biopsy and marking of the gross tumor margins and biliary or gastrointestinal bypass procedures when indicated, chest roentgenogram, upper gastrointestinal series, i.v. pyelogram, computed tomography scan, complete blood count, and blood chemistry studies including carcinoembryonic antigen, alkaline phosphatase, blood urea nitrogen, and blood glucose level determinations. To be eligible for randomization, patients had to be ambulatory and, although locally advanced, tumors had to be limited to a target volume no greater than 1,700 cm^3. Patients were excluded from this study if they had a prior malignancy except skin cancer, unless they had been disease free for 5 years; prior chemotherapy or radiation therapy; chronic renal disease; overt metastases; or acute intercurrent postoperative complications that would preclude radiation.

The study contained three treatment arms (photons, neutrons, and mixed-beam irradiation). Facilities participating in this study (Fermilab, the Cleveland Clinic Foundation, and the University of Washington) could elect to randomly assign patients to either two or three of the treatment arms but were required to participate in the photon control arm. Fermilab chose neutrons alone, while the Cleveland Clinic and the University of Washington chose mixed beam. Patients were randomly assigned through the RTOG operational office to receive either photon (control) radiation therapy, neutrons, or mixed-beam radiation therapy. Neutron doses were scaled according to the relative biologic effectiveness (RBE) calculations for the various institutions: 3.3 for the University of Washington and the Cleveland Clinic Foundation and 3.0 for Fermilab. The gamma contaminate was included in the neutron dose. Mixed-beam irradiation is a mixture of 40% neutrons and 60% photons.

Treatment plans were designed to deliver doses equivalent to 6,400 cGy at 180–200 cGy per fraction to the tumor volume in the photon or mixed-beam arms but not to exceed 5,000 cGy to the bowel outside the target volume, 2,000 cGy to the kidneys, 4,000 cGy to the spinal cord, or 3,500 cGy to the liver. When patients were randomly assigned to receive neutrons alone, the same equivalent doses were employed, but the treatment was delivered in 15 fractions over 7 weeks. The target volume was specified as covering the gross disease with a 2-cm margin. The recommended left lateral margin was 3 cm to encompass a greater volume of the pancreas, as pancreatic cancers may spread along the pancreas in an occult fashion. After the equivalent of 4,500 cGy, the fields could be reduced to a margin of 1–2 cm around the gross disease.

TABLE 1. *Patient characteristics*

	Therapy, no. of patients		
	Photons	Neutrons	Mixed beam
Total no. of patients	23	15	11
Sex			
male	14	6	5
female	9	9	6
Histology			
adenocarcinoma	23	14	9
islet cell carcinoma	0	1	2
Differentiation			
well	5	4	2
moderate	11	6	5
poor	4	3	4
unknown	3	2	0
Location			
head	16	10	4
body	1	1	1
tail	0	1	0
body and tail	1	1	1
head and body	5	1	5
diffuse	0	1	0
Karnofsky value			
60–70	4	1	3
80–90	14	14	6
100	5	0	2
Tumor size, cm^2			
1–40	15	10	8
41–80	6	3	3
80–160	1	1	0
unknown	1	1	0
T stage			
T_1	0	0	1
T_2	7	4	2
T_3	4	3	4
T_4	12	8	4
N stage			
N_0	8	9	6
N_1	9	4	3
N_2	2	0	1
N_x	4	2	1

The quality of the radiotherapy was ensured by a central review of localization films and treatment plans. Data were reviewed at a central office by data managers and the study chairman.

The efficacy of the treatment was evaluated by comparing the duration of local control, the overall survival rate, and the disease-free survival rate. In each instance, Kaplan–Meier plots were generated and compared using the Mantel–Haenszel test. The survival rate was measured as absolute survival from the start of treatment. For the evaluation of local control, patients in whom there was a persistence of disease at the time of the first follow-up visit were considered to have local failures from day 1. For the calculation of the disease-free survival rate, death was not considered failure, but cases were censored at the time of death.

The acute reactions during treatment and the long-term serious complications were recorded prospectively using the RTOG acute morbidity scoring criteria and the RTOG late radiation morbidity scoring scheme, respectively.

RESULTS

The major end points of this study are local/regional control, survival, and disease-free survival rates. Complication rates and tolerance of the irradiated tissue are secondary end points.

Table 1 shows that, of the major patient characteristics, there were no significant differences in the distribution of pretreatment factors among the three treatment groups.

Figure 1 shows the fractional survival rate by treatment arm as a function of time. The median survival duration of the entire group (n = 49) is 7.1 months, with no patient alive at 2 years. The median survival duration by treatment arm is 5.6 months with neutrons (n = 15); 7.8 months with mixed-beam radiation (n = 11), and 8.3 months with photons (n = 23). A Mantel–Haenszel test was performed to compare these curves; th· p value is 0.1.

The median duration of local control of all patients in this study is 4.3 months (n = 49). The local control

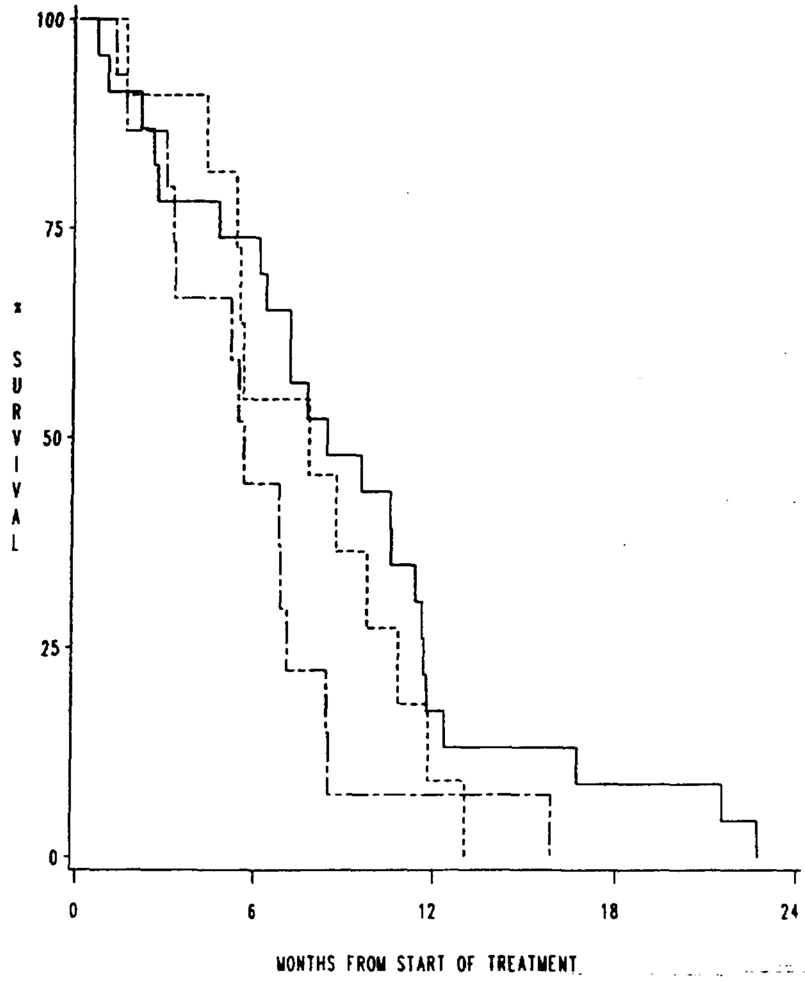

FIG. 1. RTOG 7921 Survival rate by treatment (n = 49). Photons (——), n = 23. Mixed beam (- - -), n = 11. Neutrons (- — -), n = 15. P = 0.10.

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rate is shown in Fig. 2. Persistent disease at the time of the first follow-up evaluation was more common among patients treated with photons (43%) than with either neutrons (13%) or mixed-beam radiation (18%), but the three curves converge by about 7 months. This observation is reflected in the median duration of local control: 6.7 months with neutrons (n = 15), 6.5 months with mixed-beam therapy (n = 11), and 2.6 months with photons (n = 23). However, a comparison of these curves employing a Mantel–Haenszel test revealed no significant difference among the treatment arms.

The disease-free survival rate is shown in Fig. 3. For the entire group (n = 49), the median disease-free survival time is 3.7 months. Using the Mantel–Haenszel test, there are no significant differences among the treatment arms, with disease-free survival times of 3.7, 3.4, and 3.7 months for patients treated with neutron, mixed-beam, and photon therapy, respectively.

The short-term reactions to therapy were similar in all arms of the study (Table 2). Minor reactions were somewhat more common in the experimental arms. Four patients (one photon, two mixed beam, and one neutron) had severe nausea and vomiting; in the neutron patient, this was accompanied by severe diarrhea. One patient in the photon arm had life-threatening nausea and vomiting.

The frequency of late complications of treatment is difficult to evaluate given the few patients at risk beyond 1 year. Nevertheless, it does appear that the risk was higher in patients treated with neutrons (Table 3). One patient treated with neutrons experienced life-threatening liver and small bowel complications. Another patient experienced moderate stomach, small bowel, and large bowel complications. A third patient experienced moderate liver and severe stomach reactions. Only one patient treated with photons experienced a moderate small bowel reaction, and none had a severe late effect. Thus, the frequency of moderate or worse reactions was 4% in the photon-treated patients and 20% in the neutron-treated patients. No patient treated with mixed-beam radiation had worse than a minor late reaction.

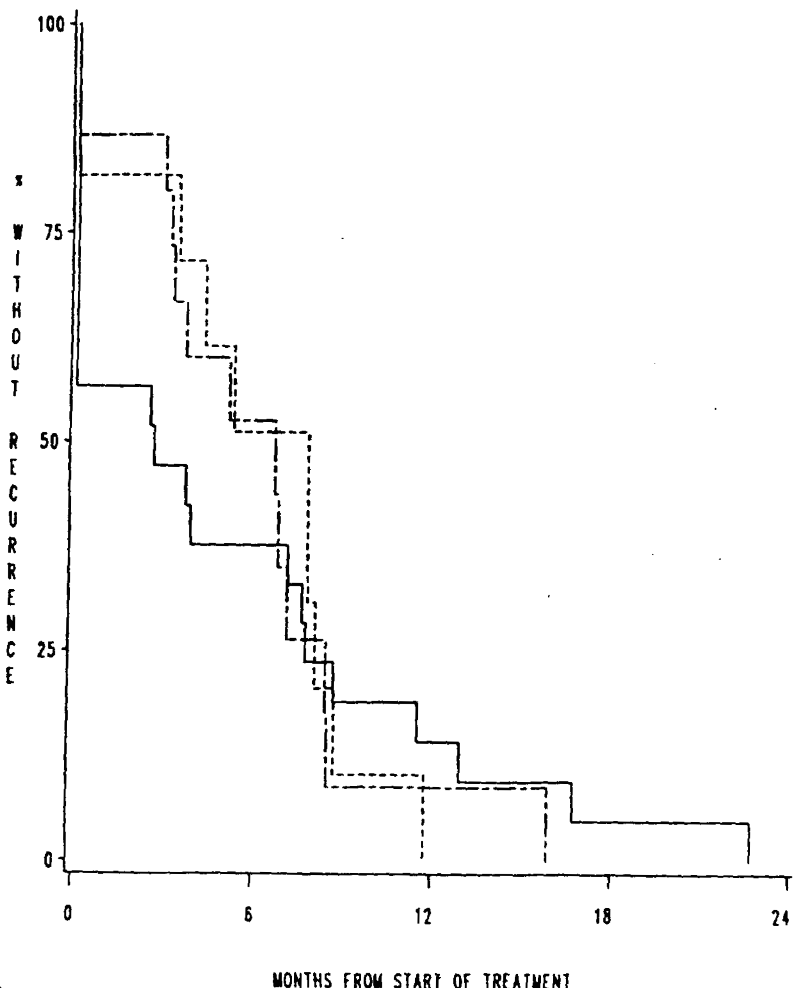

FIG. 2. RTOG 7921 Local control rate by treatment (n = 49). Group totals same as in Figure 1. P = N.S.

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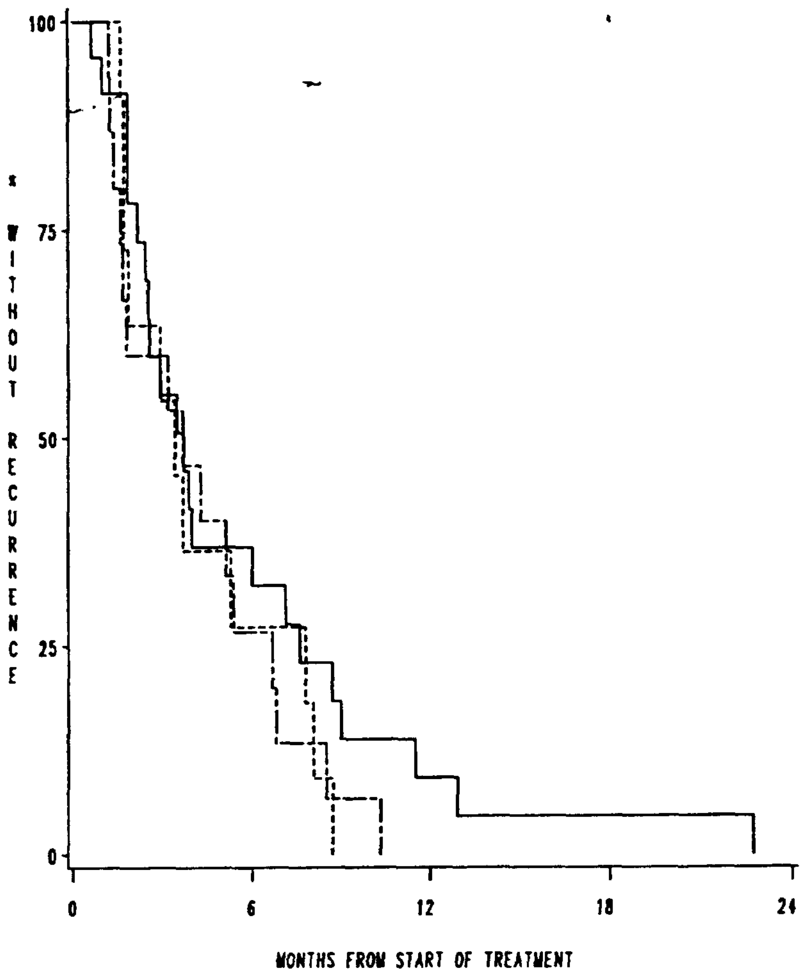

FIG. 3. RTOG 7921 Disease-free survival rate by treatment (n = 49). Group totals same as in Figure 1. P = N.S.

TABLE 2. *Acute reactions by grade*

Reaction	Grade[a], no. of patients					Total no. of patients (%)
	1	2	3	4	5	
Phototherapy (n = 23)	6	0	0	0	0	6 (26)
GI[b] (nausea/vomiting)	3	5	1	1	0	10 (43)
GI (diarrhea)	7	4	0	0	0	11 (48)
hematologic	2	0	0	0	0	2 (9)
Mixed-beam therapy (n = 11)						
skin	4	0	0	0	0	4 (36)
GI (nausea/vomiting)	4	4	2	0	0	10 (91)
GI (diarrhea)	3	3	0	0	0	6 (55)
hematologic	0	0	0	0	0	0 (0)
Neutron therapy (n = 15)						
skin	8	4	0	0	0	12 (80)
GI (nausea/vomiting)	1	4	1	0	0	6 (40)
GI (diarrhea)	7	2	1	0	0	10 (67)
hematologic	1	0	0	0	0	1 (8)

[a] 1, minor; 2, moderate; 3, severe; 4, life threatening; and 5, death.
[b] GI, gastrointestinal.

DISCUSSION

The treatment of patients with locally advanced pancreatic cancer continues to present a significant challenge. Without treatment (15) or with only conservative surgery (3), the median survival time is less than 4 months.

Dobelbower and colleagues (5,6,16) have reported a considerable improvement in survival with high-dose radiation therapy. The 1-year survival rate was 49% among patients receiving 5,900–7,000 cGy in 7–9 weeks with or without adjuvant chemotherapy. Similar results were reported by Komaki et al. (10), although in other series with high-dose radiation, the median survival time is closer to 7.0 months (2,8,17). Both adjuvant chemotherapy and techniques to increase the radiation dose to the tumor have been employed to further improve the results of therapy. The addition of chemotherapy improved the median survival time in a Gastrointestinal Tumor Study Group trial (9). Patients randomly chosen to receive 6,000 cGy had a median survival time of 23 weeks. With 6,000 cGy and

TABLE 3. *Complications by grade*

Reaction	"Grades"*, no. of patients: 1	2	3	4	5	Total no. of patients (%)
Photon therapy (n = 23)						
stomach	1	0	0	0	0	1 (4)
liver	1	0	0	0	0	1 (4)
kidney (left)	1	0	0	0	0	1 (4)
kidney (right)	1	0	0	0	0	1 (4)
small bowel	2	1	0	0	0	3 (13)
large bowel	1	0	0	0	0	1 (4)
spine	1	0	0	0	0	1 (4)
Mixed beam therapy (n = 11)						
stomach	2	0	0	0	0	2 (18)
small bowel	3	0	0	0	0	3 (27)
large bowel	1	0	0	0	0	1 (9)
Neutron therapy (n = 15)						
stomach	0	2	1	0	0	3 (20)
liver	1	1	0	1	0	3 (20)
small bowel	3	1	0	1	0	5 (33)
large bowel	1	2	0	0	0	3 (20)

* 1, minor; 2, moderate; 3, severe; 4, life threatening; and 5, death.

fluorouracil or 4,000 cGy and fluorouracil, the median survival time increased to 40 and 42 weeks, respectively. To further increase the radiation dose, both intraoperative radiation therapy (IORT) and ^{125}I implants have been employed in selected cases with or without adjuvant therapy. With IORT, the median survival time is in the range of 10–16.5 months (7,18–20) but has not been compared with that of conventional therapy in a randomized trial. With ^{125}I implants, median survival times of 11–14 months have been reported (21,22).

Despite high-dose radiation, locally persistent disease is common. Komaki et al. (10) noted that 80% of the patients with progressive disease had local failure with or without distant disease. Even with doses > 5,000 cGy by ^{198}Au implant or IORT, Rich (7) reported 77% symptomatic local failure. The addition of chemotherapy does little to alter this pattern of failure (9). Given this high local failure rate, it is reasonable to assume that improvements in local control will impact on the survival rate.

The use of neutrons in the treatment of pancreatic carcinomas is predicated on the hope that the biological advantages of neutrons would improve the local control and survival rates. In a retrospective study, both neutrons alone and mixed-beam radiation have been employed in the treatment of pancreatic cancer. In an early study, Al-Abdulla et al. (23) employed mixed-beam doses equivalent to 4,920–6,060 cGy with or without chemotherapy. Among the patients treated with neutron therapy, 40% were alive at 1 year. By comparison, historical controls treated with photons or ^{198}Au by implant had 1-year survival rates of 23 and 32%, respectively. The Mid-Atlantic Neutron Research Center (24) employed 1,700–1,750-cGy neutrons (equivalent to approximately 5,200 cGy of photons) with or without fluorouracil. The median survival time of these patients was 6 months, with 47% (nine of 19) having failure within the treatment field. Cohen, Kaul, and their colleagues (25,26) also reported a 6-month median survival time in 77 patients treated with neutron doses of 1,500–2,500 cGy. In a small series of patients treated with mixed-beam radiation to a 6,000-cGy equivalent and streptozotocin, fluorouracil, and mitomycin-C at the Cleveland Clinic (27), the median survival time was 10 months. In none of the prior studies of neutron therapy for pancreatic cancer were concurrent controls employed.

This study was designed to determine if neutron radiation alone or as mixed-beam radiation was superior to conventional radiation in the treatment of unresectable pancreatic carcinomas.

The acute toxicity encountered in the experimental arms of this study was similar to that observed with photons. The moderate or worse late complications were more frequent and more severe in the neutron arm as compared with either the photon or mixed-beam arms. Among patients treated with neutrons, the frequency of severe and life-threatening reactions was 13%; 20% of the patients experienced a moderate or worse reaction. A variety of factors may have contributed to this effect. In comparison with high-energy photon beams, the neutron beams have a wider penumbra and poorer depth dose characteristics. Some patients who received neutrons were treated in a standing position. It may have allowed a greater volume of the stomach and intestine to fall into the treatment volume than might have occurred with the conventional supine treatment position.

The median survival time and local control rate in this series is similar to those reported in other series using photons (7,8,17,28), neutrons (23–27), or heavy charged particles (29). As judged by the local control, overall survival, or disease-free survival rates, no statistically significant difference could be appreciated among the treatment arms. The further escalation of the neutron dose or, in the case of mixed-beam radiation, increasing the proportion of the dose delivered with neutrons does not seem warranted based on the complication rate experienced in the neutron arm.

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