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Evaluation of a Neutron Boost in Head and Neck Cancer

Results of the Randomized RTOG Trial 78–08

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Patients with untreated squamous cell cancer of the head and neck region were randomized to receive either a boost of 25–30 Gy using photon-beam irradiation (photons) or an equivalent boost using neutron-beam irradiation (neutrons). All patients received an initial 45–50 Gy of wide-field photon irradiation. A total of 57 patients was evaluable on the neutron arm and 58 were evaluable on the photon arm. The proportion of patients with complete responses was 60 and 64% on the neutron and photon arms, respectively. The locally disease-free proportion at 2 years was estimated to be 20 and 31%, and the 2-year survival was estimated to be 32 and 41%, respectively. These differences are not statistically significant. There was a higher rate of severe complications on the neutron arm, 16 versus 7%. Thus, there was no evidence that a neutron boost produces better initial tumor clearance, local tumor control, or survival than a photon boost, and it may produce more complications.

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The radiobiological advantages of neutron therapy over conventional radiation are well known. The dense ionization caused by neutrons leads to more effective killing of cells protected by hypoxia or by virtue of their position in a relatively resistant phase in the cell cycle. Furthermore, repair mechanisms that take place after conventional radiation are not effective following neutron radiation.

Early experience with neutron therapy for head and neck cancer in the United States resulted in a high complication rate (4,8–10). This experience led to the choice of a mixed-beam schedule of neutrons and photons for investigation in the major phase III Radiation Therapy Oncology Group (RTOG) protocols. This combination of beams seems logical because only a proportion of the cells in the tumor is resistant to conventional radiation. The partial use of neutron radiation only in the quantity necessary to control the resistant portion of the tumor reduces the late effects in the normal tissues, known to be more severe with neutrons (14).

In another study (RTOG 76–10), the investigative arm was neutrons and photons given in a mixed schedule throughout the treatment. The present study (RTOG 78–08) was designed to determine whether a neutron boost delivered sequentially after 45–50 Gy of photons would be superior to photons alone for the definitive treatment of carcinoma of the head and neck region.

MATERIALS AND METHODS

Patients with untreated squamous cell cancer of the head and neck region who were considered for treatment using radiation therapy alone were selected. The patients had to have a stage of T_2 or greater with any N stage but no distant metastases. Patients with more than one tumor or Karnofsky status less than 50 were excluded. Randomization between the neutron boost arm and the photon boost arm was stratified by institution, T-stage, and region and was performed by a central office. Randomization could be done any time before the boost was started.

All patients initially received 45–50 Gy photons delivered in daily fractions of 1.8–2 Gy. Photons were to be delivered using equipment operating at 4.0 MeV or greater or ^{60}Co with a minimum source-to-skin distance (SSD) of 80 cm. The neutron boost was to include only areas involved by gross tumor, primary, or nodes plus a margin of 2 cm (90% contours). The boost was to be given in four to six fractions in 2–3 weeks. The neutron dose depended on the radiobiological effectiveness (RBE) determined at the institution and was to be equivalent to 25–30 Gy photons. The photon boost was to include areas with gross tumor plus a 1 cm margin (2 cm with cobalt). The boost was to be 25–30 Gy administered over 2–3 weeks in five daily fractions per week. An interstitial implant was allowed in appropriate cases for delivery of the boost. Five patients in the control arm and one patient assigned to neutrons, all with oral cavity cancers, received an interstitial implant. In both arms of the study, the total aim was to deliver 75 Gy, or the equivalent, to the tumor.

The quality of the radiotherapy was ensured by a central review of localization films and treatment plans within 7 days of randomization. Institutions with errors were to be notified in enough time to allow correction. Data were reviewed by data managers at a central office and by the study chairman.

The efficacy of the two treatments was evaluated as follows: by comparing the proportion of patients undergoing each treatment who had initial local clearance of the tumor after radiotherapy; by comparing the proportion of patients in each treatment group who remained free of disease in the head and neck; and by comparing the proportion of patients alive in each treatment group. The latter two comparisons were made by using the Kaplan-Meier method to estimate the distributions of time to local failure and survival time. Patients whose tumor never cleared were considered as a local failure on the first study day. Tests of significance were made using the log-rank test. In the computation of time to local failure, patients who died with no evidence of local disease were considered to be censored. The mean follow-up time for all patients is 33 months.

The safety of the treatments was evaluated by comparing the long-term serious complications between the two treatment arms.

RESULTS

The study was open for patient accrual from October 1978 to August 1982, and 118 patients were registered. Two patients with no follow-up information and one patient who did not have squamous cancer were excluded. Of the 115 remaining patients, 57 were treated with a neutron boost and 58 with conventional irradiation.

Table 1 shows that the major patient characteristics were equally distributed in the two treatment groups. Other characteristics including age, time to first symptom, performance state, and nutrition state were also about the same in the two study arms.

TABLE 1. *Patient Characteristics by Treatment*

	Neutrons	Photons	Total
No. of patients	57	58	115
Sex–male (%)	75	83	79
Region			
Hypopharynx	9	9	9
Nasopharynx	2	2	2
Oral cavity	25	28	26
Oropharynx	53	50	51
Supraglottic larynx	12	12	12
T-stage			
T_2	37	38	37
T_3	40	38	39
T_4	23	24	23
N-stage			
N_0	42	40	41
N_1	18	16	17
N_{2A}	11	12	11
N_{2B}	7	9	8
N_{3A}	7	10	8
N_{3B}	16	12	14
N_{3C}	0	2	1
Differentiation			
Low grade	32	21	26
Intermediate grade	54	45	50
High grade	8	21	15
Unknown	5	14	10
Infiltration			
Exophytic	18	16	17
Superficial	5	7	6
Moderately infiltrating	39	36	37
Deeply infiltrating	32	34	33
Unknown	7	7	7

A total of 60% of the patients undergoing a neutron boost achieved clearance of local disease compared with 64% of those having a photon boost. There was no significant difference between the neutron boost and the photon boost arms by any patient characteristic, stage of disease, or tumor site (Table 2). Oral cavity tumors responded least to neutron therapy, but this was not statistically significant.

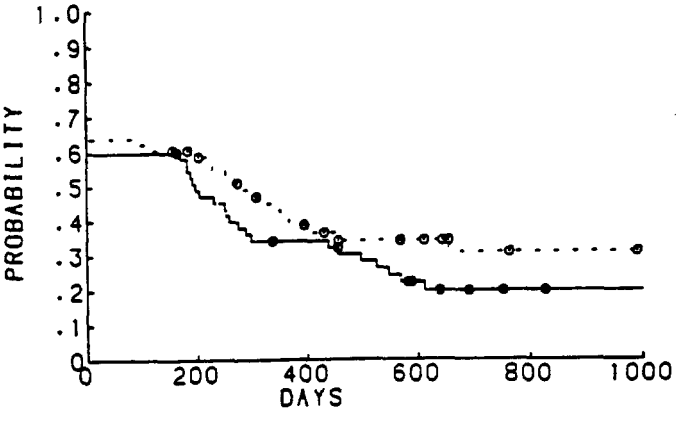
A stepwise logistic regression was used to determine which variables in Table 1 were prognostic of tumor clearance (13). Only characteristics that occurred in over 10% of the patients were considered. For the total population, clearance was significantly ($p < 0.05$, two-sided) affected by T-stage (T_2 versus $>T_2$), extent of infiltration, performance status, and cell differentiation (low grade versus other).

The 2-year local tumor-free rate of patients receiving the neutron boost was 20% compared with 31% for patients receiving a photon boost. This difference was not significant. A 90% confidence interval on the difference in the 2-year local tumor-free rates between neutron and photon boost patients was −26 to 4%. If only patients who achieved tumor clearance are considered, the 2-year local tumor-free rates are 33 and 49%, respectively, and again the difference is not significant. Ten patients who have no evidence of disease have not been followed for 2 years yet, so the 2-year local control rates may change slightly with further follow-up. Figure 1 shows local tumor-free interval by treatment.

A stepwise Cox regression model was used to determine the factors that were prognostic for tumor-free

TABLE 2. *Local Clearance by Treatment and Prognostic Characteristics*

	Treatment					
	Neutrons		Photons		Total	
Characteristics	%	No. of patients	%	No. of patients	%	No. of patients
T-stage						
T_2	90	21	86	22	88	43
T_3	48	23	59	22	53	45
T_4	31	13	36	14	34	27
Differentiation						
Low grade	44	18	33	12	40	30
Intermediate grade	65	31	73	26	69	57
High grade	80	5	83	12	82	17
Unknown	67	3	50	8	55	11
Karnofsky status						
50–70	29	7	25	4	28	11
80	44	16	47	17	46	33
90–100	74	34	76	37	75	71
Infiltration						
Exophytic	90	10	100	9	95	19
Superficial	67	3	100	4	86	7
Moderately infiltrating	68	22	67	21	68	33
Deeply infiltrating	33	18	40	20	37	38
Unknown	50	4	50	4	50	8
Region						
Hypopharynx	60	5	100	5	80	10
Nasopharynx	0	1	0	1	0	2
Oral cavity	36	14	62	16	50	30
Oropharynx	67	30	55	29	61	59
Supraglottic larynx	86	7	86	7	86	14
N-stage						
N_0	63	24	74	23	68	47
N_1	80	10	67	9	74	19
N_{2A}	50	6	71	7	61	13
N_{2B}	50	4	40	5	44	9
N_{3A}	75	4	83	6	80	10
N_{3B}	33	9	29	7	31	16
N_{3C}	0	0	0	1	0	1



TREATMENT	NED	FAIL.	TOTAL	MEDIAN
—— NEUTRONS	13	44	57	197.0
- - - PHOTONS	21	37	58	280.0

FIG. 1. Local tumor-free survival by treatment.

survival. The same factors as those for tumor clearance were selected, but in addition N-stage (N_{3B} versus other) was also prognostic. Table 3 shows 2-year local tumor-free rates by treatment for these patient characteristics.

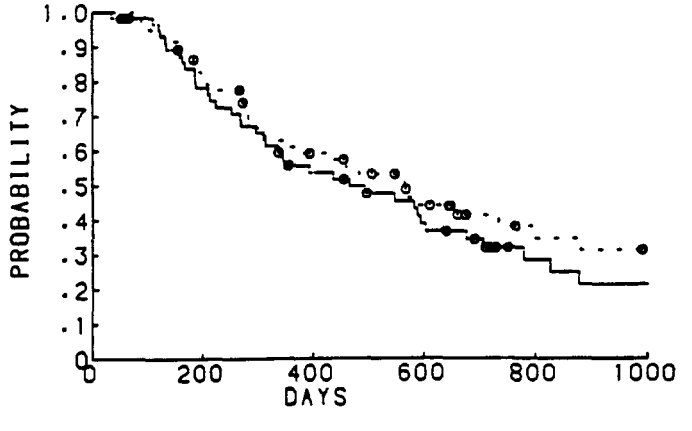
Of the 34 patients who achieved tumor clearance and did not suffer local recurrence, 10 had distant recurrence or second primary (5/13 undergoing neutron therapy; 5/21 undergoing photon therapy).

The 2-year survival rates are 32 ± 7% and 41 ± 7% for neutrons and photons, respectively. This difference is not significant. Figure 2 shows survival by treatment.

Table 4 lists the complications of each treatment. Only serious complications were considered.

DISCUSSION

After the Hammersmith experience (3), only one study showed an advantage for neutrons (7). This recent study, however, had a very low accrual and the outcome of patients treated with photons was extremely poor. Other randomized trials comparing neutrons or mixed beam with photons in head and neck cancer failed to show an advantage for neutrons (1,6,11). Various reasons were put forward to explain this disappointment including the inferior versatility of systems that deliver neutrons, their suboptimal physical beam characteristics compared with photons, and most important, the



TREATMENT	ALIVE	DEAD	TOTAL	MEDIAN
—— NEUTRONS	18	39	57	466.0
- - - PHOTONS	24	34	58	565.0

FIG. 2. Survival by treatment.

TABLE 3. *Two-year Local Tumor-free Rates by Treatment and Patient Characteristics*

	Treatment					
	Neutrons		Photons		Total	
	Rate (%)	S.E. (%)	Rate (%)	S.E. (%)	Rate (%)	S.E. (%)
All patients	20	6	31	7	25	4
T-stage						
T_2	25	11	51	11	37	8
T_3	22	9	25	10	24	7
T_4	7	7	11	9	9	6
Differentiation						
Low grade	0	0	8	8	4	4
Intermediate grade	21	8	30	10	24	7
High grade	60	22	56	15	57	12
Unknown	33	27	37	17	36	15
Karnofsky status						
50–70	0	0	25	22	9	9
80	23	11	25	11	24	8
90–100	22	8	34	9	28	6
Extent of infiltration						
Exophytic	24	15	76	15	48	12
Superficial	33	27	75	22	57	19
Moderately infiltrating	28	10	11	9	21	7
Deeply infiltrating	5	5	14	9	10	5
Unknown	25	21	50	25	38	17
Region						
Hypopharynx	40	22	100	0	69	15
Nasopharynx	0	0	0	0	0	6
Oral cavity	0	6	6	6	4	4
Oropharynx	23	8	32	9	28	6
Supraglottic larynx	43	19	54	20	47	14
N-stage						
N_0	26	9	32	10	28	7
N_1	20	13	44	17	30	11
N_{2A}	17	15	54	20	33	14
N_{2B}	25	22	20	18	17	14
N_{3A}	25	22	62	21	44	17
N_{3B}	6	0	0	0	0	0
N_{3C}	0	0	0	0	0	0

S.E., standard error.

lack of patient selection in all past clinical experience. It is currently believed that neutrons should be applied selectively to tumors more likely to respond to this treatment than to conventional radiation. The present study (RTOG 78–08) was designed to minimize these shortcomings by delivering neutrons as a boost only and to a reduced volume. An element of selection was introduced by allowing randomization up to the time when the boost was delivered in the sixth week of treatment. Patients who were referred to this trial were judged to have an unsatisfactory response of their tumor to the initial photon component of the treatment, a feature associated with an unfavorable outcome (2). This selection of patients led to poorer results. In another study, when randomization was performed before any treatment, the 2-year disease-free survivals were 26 and 37% for mixed beam and photons (6). In the present study, which had earlier disease by T stage, the

TABLE 4. *Complications by Treatment*

	Neutrons	Photons
Soft tissue necrosis	4	3
Bone necrosis	4[a]	0
Radiation caries	1	1
Fistula formation	2	0
Total complications	11	4
Total patients	9 (16%)	4 (7%)

[a] Two patients with bone necrosis had also another complication—soft tissue necrosis in one and radiation caries in another.

rates were 20 and 31% for neutron boost and photons, respectively.

Patients treated with a neutron boost did somewhat worse in terms of local control, survival, and complications than patients treated with photons alone. This result can be explained if no subpopulation of patients with squamous carcinoma of the head and neck can advantageously be treated with neutrons. Assuming, however, that such a subpopulation exists, one may criticize the low dose of the neutron boost or its timing. Based on a theoretical model, Denekamp et al. (5) contend that when hypoxic cell sensitizers are given with photons, it should be administered early in the treatment rather than at its end. Maruyama et al. (12) also recommend scheduling the use of intracavitary neutron therapy before fractionated external beam photon therapy. Finally, the clinical criterion of tumor response during the course of photon therapy, as exercised in this study, may not be sufficient. More reliable predictive assays need to be developed before the theoretical advantages of neutron therapy in head and neck cancer can be unmasked. ℭ

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