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● Original Contribution

FAST NEUTRON IRRADIATION OF METASTATIC CERVICAL ADENOPATHY: THE RESULTS OF A RANDOMIZED RTOG STUDY

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Between 1977 and 1982, 199 evaluable patients with measurable cervical adenopathy were entered on a prospective, randomized RTOG study evaluating the use of fast neutrons in treatment of advanced, inoperable squamous cell carcinomas of the head and neck region. One hundred-eleven patients were randomized to receive mixed beam radiation therapy, and 88 were randomized to the photon control treatment. The complete response rates were 86% for mixed beam vs 75% for photons for Stage N₁ nodes, 62% for mixed beam vs 48% for photons for Stage N₂ nodes, and 63% for mixed beam vs 53% for photons for N₃ nodes. The percents of patients remaining free of their adenopathy for two years were 78% for mixed beam vs 55% for photons for Stage N₁ nodes, 39% for both mixed beam and photons for N₂ nodes and 24% for mixed beam vs 13% for photons for N₃ nodes. The median disease-free status was 20.3 months for mixed beam treated patients and 6.4 months for photon-treated patients. Patients who had clearance of cervical adenopathy survived significantly longer than those who did not.

High LET, Radiation therapy, Neutrons, Head and neck cancer, Mixed beam, Cervical lymph nodes.

INTRODUCTION

Following Stone's early work at Berkeley,⁹ research in the field of fast neutron treatment of human malignancies was restarted in this country in 1971. After six years' work with Phase I studies, randomized Phase III trials were begun in 1977. One of the sites of interest for these studies has been cervical neck nodes.

The management of patients with neck node metastasis from advanced head and neck carcinomas remains a difficult clinical problem. These lesions are often not amenable to surgical intervention, and are often uncontrollable by conventional photon radiation therapy. Based on encouraging results of pilot studies both from this country and from Europe,^{1,2,3,4,8} a Phase III randomized trial using fast neutron radiation therapy was formulated with the hope of improving the results of treatment in this group of patients.

Metastatic cervical lymphadenopathy from advanced squamous cell carcinomas of the head and neck serves as an excellent *in vivo* test site to evaluate the results of fast neutron beam radiation therapy. The tumor volume is

easily measured so that the original volume of disease and the subsequent response to treatment can be accurately assessed. This report compares the results of fast neutron irradiation given in a "mixed beam" fractionation schedule with conventional photon radiation therapy in this test system.

METHODS AND MATERIALS

Between 1977 and 1982, 352 patients were entered on a prospective, randomized RTOG study comparing fast neutron radiation therapy, mixed beam radiation therapy and standard photon radiation therapy for inoperable, advanced squamous cell carcinomas of the head and neck. The major endpoints were survival and tumor control.

Eligible patients were randomized by calling a central office. Stratification was based on the stage of the tumor and the primary site. Patients were also balanced with respect to participating institutions.

Shortly after the study was opened, the fast-neutron-only treatment was discontinued due to low patient accrual. Since only 26 patients were randomized to that

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Table 1. Administrative data

	Photon	Mixed beam	Neutron
Patients entered*	149	177	26
Ineligible	5	6	
Cancelled	2	5	
Insufficient data	5	2	
Stage N ₀	49	53	
Patients analyzed	88	111	

*Randomization was purposely unbalanced.

treatment regimen, it will be excluded from further consideration in this report.

The treatments were as follows: *Photons* (control): 66–74 Gy megavoltage photon irradiation. The treatment was given in 1.8–2 Gy daily fractions, 5 fractions per week, 9–10 Gy per week to all sites of disease. The uninvolved neck and supraclavicular regions received 46–50 Gy. The total treatment was delivered over 7–8 weeks; *Mixed beam*: 40–44 Gy megavoltage photons plus 7.5–10 Gy_{n_r} neutrons. Three fractions of photons plus 2 fractions of neutrons were given each week. Photons were given in 1.8–2 Gy fractions, and neutrons were given in fractions equivalent to 1.8–2 Gy photon irradiation. The equivalent doses were based on the RBE for each facility. Mixed beam irradiation was delivered to all sites of disease. The uninvolved neck and supraclavicular regions received 46–50 Gy photon irradiation. The total treatment was delivered over 7–8 weeks.

A total of 352 patients entered the study. Of these, 26 were randomized to the neutron-only treatment. Eleven patients proved to be ineligible, 7 were cancelled, 7 had insufficient data submitted to study headquarters and 102 were staged N₀. There remain 199 analyzable patients with clinically positive neck nodes. (Table 1)

Patients were referred to one of five participating neutron facilities: The University of Washington, GLANTA, MANTA, TAMVEC, and The Fermilab. The methods of neutron production and RBE-adjusted dose recommendations for the neutron portion of mixed beam treatment are listed in Table 2.

Follow-up examinations were reported at three-month intervals, starting with Day 90 (Day 1 is the first day of treatment), for two years, and then at six-month intervals for the subsequent three years. The status of the cervical adenopathy was assessed on each follow-up report.

Data quality was ensured by carefully checking forms at the RTOG Statistical Center. The radiotherapy treatment plans were reviewed by a panel of radiotherapists. All relevant data for each patient were summarized by the Statistical Center and verified by a review of the patients' records by the study chairman.

Table 3 lists the patients with cervical adenopathy by N stage and treatment. The American Joint Committee for Cancer Staging and End Results Reporting System (1977) was used.

Table 2. Facility RBE adjusted neutron doses

Facility	Machine	Neutron reaction	RBE adjusted neutron dose
U of W	Cyclotron	22 MeV _{d-Bc}	7.5 – 9 Gy _{n_r}
GLANTA	Cyclotron	25 MeV _{d-Bc}	7.65– 9.2 Gy _{n_r}
MANTA	Cyclotron	35 MeV _{d-Bc}	7.7 – 9.3 Gy _{n_r}
TAMVEC	Cyclotron	50 MeV _{d-Bc}	8 – 9.5 Gy _{n_r}
Fermilab	Linac	66 MeV _{p-Bc}	8.5 – 10 Gy _{n_r}

Table 3. N-stage by treatment

Stage	Photon	Mixed beam
N1	16	30
N2	29	29
N2A	18	13
	11	16
N3	43	52
N3A	10	12
	31	40
N3C	2	0

Table 4. Complete response of nodal disease by treatment and stage

Stage	Mixed beam %	Photon %
N1	86	75
N2	62	48
N3	63	53
All patients	69	55

$p = .025$.

Table 5. Complete response of nodal disease by treatment and substage

Stage	Mixed beam		Photon	
	%	(No.)	%	(No.)
N1	87	(26/30)	75	(12/16)
N2A	62	(8/13)	50	(9/18)
N2B	63	(10/16)	45	(5/11)
N3A	42	(5/12)	40	(4/10)
N3B	70	(28/40)	55	(17/31)
N3C	—	(0/ 0)	100	(2/ 2)

Table 6. Percent of patients remaining disease free at two years by treatment and stage

Stage	Mixed beam	Photon
N1	78%	55%
N2	39%	39%
N2A	22%	44%
	56%	23%
N3	24%	13%
N3A	42%	15%
	23%	0%
N3C	—	100%
All patients	46%	33%

$p = .03$.

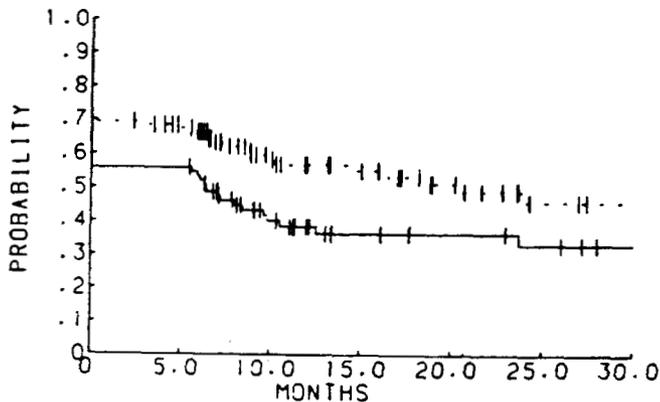
RESULTS

Table 4 lists the complete response rates by stage and treatment. The overall results favor the mixed beam treatment and, based on a one-sided chi-square test, are statistically significant ($p = .024$). Table 5 gives a further breakdown of the results by sub-stage. Although the numbers are too small in each subgroup to meaningfully evaluate significant differences, the Mantel-Haenszel test,⁷ which evaluates stratified results by looking at each N-stage separately and then combining them into a single test, again results in a statistically significant advantage for mixed-beam-treated patients ($p = .034$).

Table 6 displays the proportion of patients free of adenopathy two years after irradiation by treatment and stage as estimated by the Kaplan-Meier product limit method.⁶ The advantage for mixed beam is statistically significant ($p = .03$). Figure 1 plots the duration of response for the total group of patients. The median lymph node disease-free status is 20.3 months for mixed-beam-treated patients and 6.4 months for photon-treated patients. The difference is statistically significant ($p = .026$).

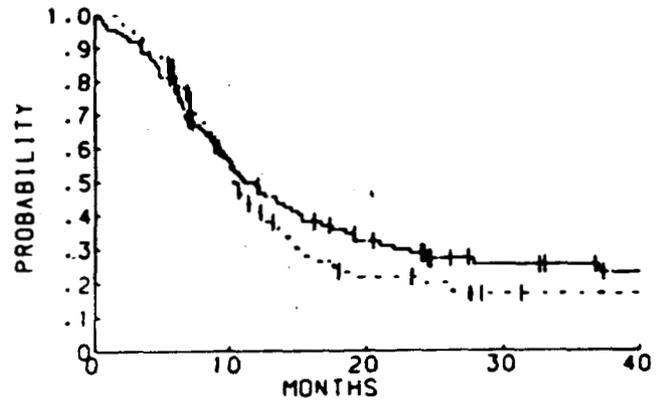
Figure 2 shows the survival experience by treatment for this group. The curves are not significantly different ($p = .38$, logrank); however, there does appear to be a trend favoring the mixed beam group. This trend can be explained by Figure 3 in conjunction with the significantly higher complete nodal response rate in patients randomized to mixed beam.

Figure 3 is a plot of survival by whether patients achieved nodal clearance. Patients who died or were lost to follow-up before four months were taken out of this analysis since the inclusion of patients who were not followed long enough to clear would produce a spuriously significant result. The difference between the curves is highly significant ($p < .0001$, logrank); i.e. patients who



TREATMENT	TOTAL	FAILURES	MEDIAN
— Photons	88	54	6.4
-- Mixed Beam	111	50	20.3

Fig. 1. Duration of complete response.



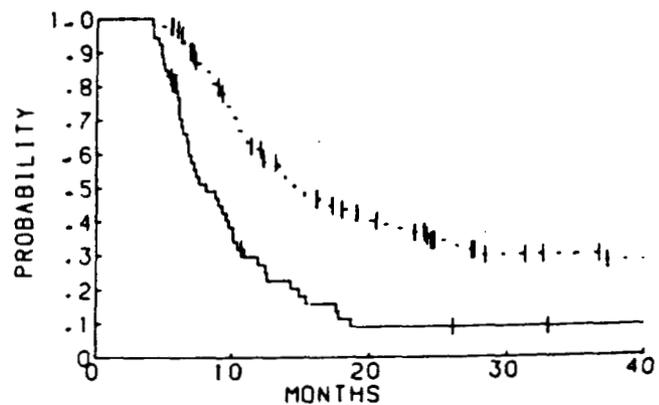
TREATMENT	TOTAL	ALIVE	DEAD	MEDIAN
— Mixed Beam	111	35	76	11.1
----- Photons	88	24	64	10.4

Fig. 2. Survival by treatment for patients with cervical adenopathy.

have a complete clearance of cervical adenopathy survive longer than those who do not. Therefore, mixed beam, which has a greater clearance rate, will also tend to improve survival.

DISCUSSION

Metastatic cervical lymphadenopathy from squamous cell carcinomas of the head and neck serves as a near ideal *in vivo* test system for evaluating fast neutron radiation therapy in a human malignancy. The tumor volume is



NODE CLEARANCE	TOTAL	ALIVE	DEAD	MEDIAN
— No	52	9	43	8.1
----- Yes	124	49	75	14.6

Fig. 3. Survival by clearance of nodes (restricted to patients surviving at least 4 months).

easily measured, the results of treatment can be determined accurately, and there is a reasonable data base describing the results of conventional treatment. Previous reports outlining the results of neutron therapy in this test system have been encouraging.^{2,4,5}

The results of this randomized study indicate that

mixed beam irradiation as given in this RTOG protocol is superior to conventional photon radiation therapy for the treatment of cervical adenopathy from squamous cell carcinomas of the head and neck region. The relation between complete response of cervical adenopathy and improved survival has also been demonstrated.

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