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MIXED NEUTRON/PHOTON IRRADIATION OF UNRESECTABLE SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK: THE FINAL REPORT OF A RANDOMIZED COOPERATIVE TRIAL

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Three hundred and twenty-seven patients with inoperable squamous cell carcinomas of the head and neck were entered on a randomized study comparing a mixture of neutron and photon ("mixed beam") radiation therapy with photon/electron radiation therapy. Neutron treatment was delivered with fixed-beam, physics-laboratory-based equipment. Patients with histologically proven tumors of T-stage T_2, T_3, or T_4 and any N-stage were eligible for randomization. Primary tumor sites were limited to cancers originating in the oral cavity, oropharynx, supraglottic larynx, or hypopharynx. Patients entered on this study now have a minimum at-risk follow-up period of 6 years. Study results reveal no significant differences in overall loco-regional tumor control rates or survival. Subgroup analysis reveals significant differences based on whether or not patients presented with positive lymph nodes. Loco-regional tumor control rates for patients presenting with positive lymph nodes were 30% for mixed-beam-treated patients versus 18% for photon-treated patients ($p = 0.05$). Loco-regional tumor control rates for patients presenting without positive lymph nodes were 64% for photon-treated patients and 33% for mixed-beam-treated patients ($p = 0.004$). Control of tumor located in the nodal sites favored mixed beam over photons by a margin of 45% (49/109) to 26% (23/87) with a significance of $p = 0.004$. Possible explanations for these contradictory findings are discussed.

Neutrons, Mixed beam, Head and neck cancer.

INTRODUCTION

Based on theoretical biological advantages related to their high linear energy transfer (LET) compared to low LET photons and electrons, fast neutrons have been investigated in the treatment of squamous cell carcinomas of the head and neck. The specifics of these advantages have been previously detailed (8), but in brief, there are three main advantages of fast neutrons over low LET radiations:

1. Fast neutrons are better able to kill hypoxic cells. In particular, oxygen enhancement ratios are approximately 1.6 for neutrons compared to 2.5–3.0 for conventional radiation.
2. Damage inflicted by fast neutrons is less readily repaired by cells. This holds true both for sublethal damage and potentially lethal damage.
3. There is less variation in radiosensitivity across the cell cycle as a function of delivered physical dose with high LET radiations compared to low LET radiations.

Whether these properties are relevant to a given clinical situation depends on the extent of tumor hypoxia, the capacity for damage repair, and the cycling properties of tumor cells compared with dose-limiting normal tissues in the treatment volume.

Based on these properties and on prior Phase I–II clinical studies, a Phase III clinical trial testing a mixture of neutrons and photons ("mixed beam irradiation") against conventional photon/electron radiation therapy in patients with unresectable squamous cell carcinomas of the head and neck was started in cooperating neutron treatment centers in the United States in 1977. The preliminary

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results of this study have been previously reported (4, 5). With a minimum follow-up of 6 years, this paper reports the final results of that study.

METHODS AND MATERIALS

Three hundred and twenty-seven patients with inoperable squamous cell carcinomas of the head and neck region were entered on a cooperative randomized study comparing mixed-beam radiation therapy with conventional photon/electron radiation therapy. The study was activated in February 1977 and closed in April 1982. Patients with previously untreated, histologically proven, inoperable squamous cell carcinomas of T-stage T_2, T_3, or T_4 and any N-stage originating in the oral cavity, oropharynx, supraglottic larynx or hypopharynx were eligible. Patients were ineligible if they had distant metastases, a Karnofsky performance score less than 60, or prior treatment for head and neck cancer. Eligible patients were randomized by calling a central office. Stratification was based on region and stage of the primary tumor, and the treating institution. The randomizations were intentionally unbalanced to give a greater proportion of patients the experimental treatment. Patients were referred to one of five participating neutron facilities: The University of Washington with a 22 MeV d ⟹ Be cyclotron, GLANTA with a 25 MeV d ⟹ Be cyclotron, MANTA with a 35 MeV d ⟹ Be cyclotron, TAMVEC with a 50 MeV d ⟹ Be cyclotron, and The Fermilab with a 66 MeV p ⟹ Be linear accelerator. The RBE-adjusted dose recommendations for the neutron portion of the mixed beam treatment were published in the preliminary report (5). Patients were randomized to one of two possible treatments:

Photon (control)

66–74 Gy megavoltage photon irradiation. The treatment was given in 1.8 to 2.0 Gy daily fractions, 5 fractions per week. 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 neutrons. Three fractions of photons plus two fractions of neutrons were given each week. Photons were given in 1.8–2.0 Gy fractions and neutrons were given in fractions equivalent to 1.8–2.0 Gy photon irradiation. The actual neutron doses given were based on the relative biological effectiveness (RBE) for each facility. Mixed-beam irradiation was delivered to all sites of disease. The uninvolved neck and supraclavicular regions received a dose equivalent to 46–50 Gy photon irradiation. The total treatment was delivered over 7–8 weeks.

Patients with residual or recurrent disease 90 days or greater following primary treatment were to receive radical surgical treatment if feasible.

Table 1. Administrative data

	Photon	Mixed beam	Total
Total entered	149	178	327
Ineligible	7	9	16
Cancelled	5	1	6
Inadequate data	3	5	8
Cases analyzed	134	163	297

Two hundred and ninety-seven of the 327 patients randomized on the study were eligible for this analysis. Sixteen patients were ineligible, six were cancelled, and data were inadequate on eight (Table 1). These numbers differ from the preliminary report in that ten additional patients were excluded. Retrospective review found them mainly to be ineligible because of low Karnofsky performance score or a glottic primary tumor site. One case previously listed as cancelled is now listed as ineligible. Pretreatment characteristics as a function of treatment are listed in Table 2. Follow-up examinations were reported at 3-month intervals for 2 years, at 6-month intervals for the subsequent 3 years, and then annually. All patients potentially had a minimum follow-up of 6 years. The radiotherapy treatment plans, simulation films, and port films were reviewed and verified by the study chairman.

Table 2. Pretreatment characteristics as a function of treatment

	Mixed beam %	Photon %
Sex		
Male	70	68
Female	30	32
Age		
<50	12	13
50–59	28	34
60–69	37	40
>70	23	14
Karnofsky score		
60	7	4
70	10	15
80	30	22
90	50	47
100	3	11
Region of primary		
Oral cavity	26	28
Oropharynx	53	51
Hypopharynx	10	11
Larynx	10	10
T-Stage		
T_2	21	21
T_3	49	48
T_4	30	31
N-Stage		
N_0	33	35
N_1	18	12
N_2	18	22
N_3	31	31

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Patients were considered to have achieved initial complete primary tumor clearance if the primary disease totally disappeared following radiotherapy. Patients who achieved a complete clearance with salvage surgery for residual primary disease following irradiation were considered as failures in this analysis. A complete nodal clearance is similarly defined for patients with initial nodal disease. A patient was then considered a complete responder when both complete primary and nodal clearance were achieved. Patients who did not achieve an initial clearance of the primary tumor were considered failures on study day 1. Patients who did achieve an initial clearance of the primary tumor were considered a failure on the study day when a recurrence in the primary was first reported. Even though subsequent therapy may have cleared the recurrent disease, the patient was still considered to be a failure of treatment at the time of first reported recurrence. Nodal disease control, loco-regional control, and total disease control were similarly defined except for the designation of failure. For nodal disease control, the failure could only occur in the regional nodes. For loco-regional control, failure could occur either in the primary site or in the regional nodes. For total disease control, failure could be either regional or distant. With respect to survival analysis, a patient was considered a failure if the individual died, regardless of cause of death.

Differences in initial complete response rates between treatments were evaluated by the chi-square test (2). Differences in the distributions of time durations such as survival were evaluated by the Mantel-Haenszel test (10). All reported significance levels were based on a two-sided test and upon the randomized treatment assignment regardless of whether or not the patient started or completed the assigned treatment. Six eligible patients who were assigned to mixed beam and three patients who were assigned to photons but did not receive protocol treatment were included in this analysis. Time events were plotted as step functions using the Kaplan-Meier product-limit method (9). Time was measured from the start of treatment until the time of first failure or the time of last follow-up if the patient did not fail.

RESULTS

The initial complete primary tumor clearance rates were 63% (103/163) with mixed-beam treatment and 64% (86/134) with photon/electron treatment. The initial complete nodal clearance rates were 68% (74/109) with mixed-beam and 55% (48/87) with photons and/or electrons. The initial complete response rates were 56% (92/163) for mixed-beam patients and 58% (78/134) for photon/electron patients. The overall estimated loco-regional tumor control rates at 2 and 5 years were 27% and 23% for the mixed-beam as compared to 34% and 31% for photon and/or electron beam. This difference is not statistically significant ($p = 0.39$).

The primary tumor control illustrated by treatment is shown in Figure 1. The primary tumor control for mixed-beam patients was not significantly different than for photon patients ($p = 0.39$). While no significant difference was observed between the treatments with respect to primary tumor control, a significant advantage for mixed-beam treatment was demonstrated for long-term control of tumor in the lymph nodes. The difference as illustrated in Figure 2 was significant at the $p = 0.004$ level. The rates at 2 and 5 years were 39% and 36% for the mixed beam patients as compared to 24% and 21% for the photon/electron patients.

Primary tumor control as a function of nodal status and treatment is illustrated in Figures 3 and 4. The trend towards an advantage for mixed-beam treatment at the primary site in patients who presented with positive lymph nodes parallels the advantages seen in their nodal sites; however, a distinct disadvantage for mixed-beam treatment is observed at the primary site in patients presenting with negative nodes. Primary tumor control rates for patients presenting without positive lymph nodes were 63% and 60% at 2 and 5 years for photon/electron patients as compared to 39% and 27% for mixed-beam patients ($p = 0.006$). Primary control rates for patients presenting with positive lymph nodes were 39% and 34% at 2 and 5 years for mixed-beam patients versus 31% and 27% for photon/electron patients ($p = .29$).

Figure 5 illustrates survival by treatment assignment. The overall difference was not statistically significant ($p = 0.32$). The causes of death are listed in Table 3. Analyzing survival as a function of nodal status and treatment, Figure 6 demonstrates no significant differences in survival

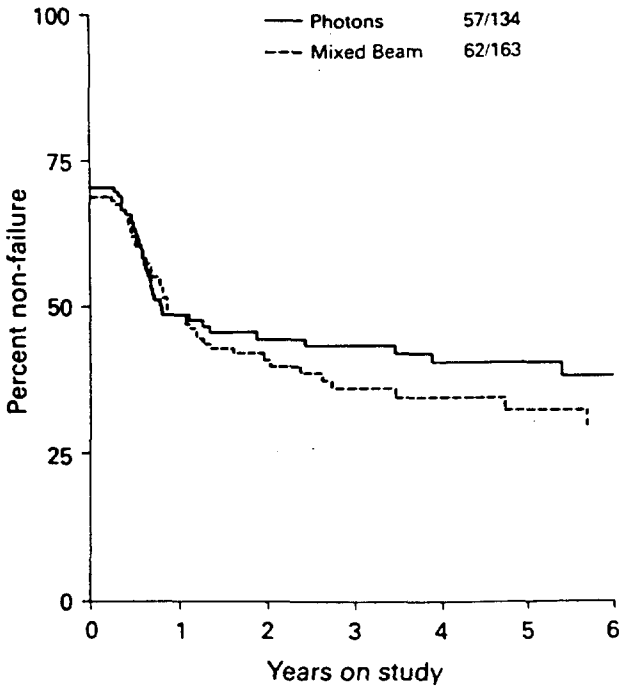

Fig. 1. Overall primary tumor control rates as a function of treatment. The difference is not statistically significant.

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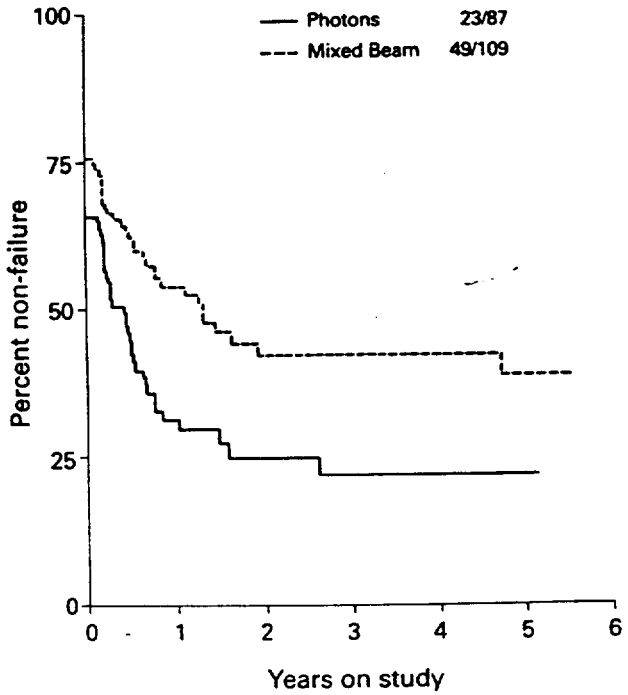

Fig. 2. Tumor control rates in the lymph nodes as a function of treatment. The difference is significant at the $p = 0.004$ level.

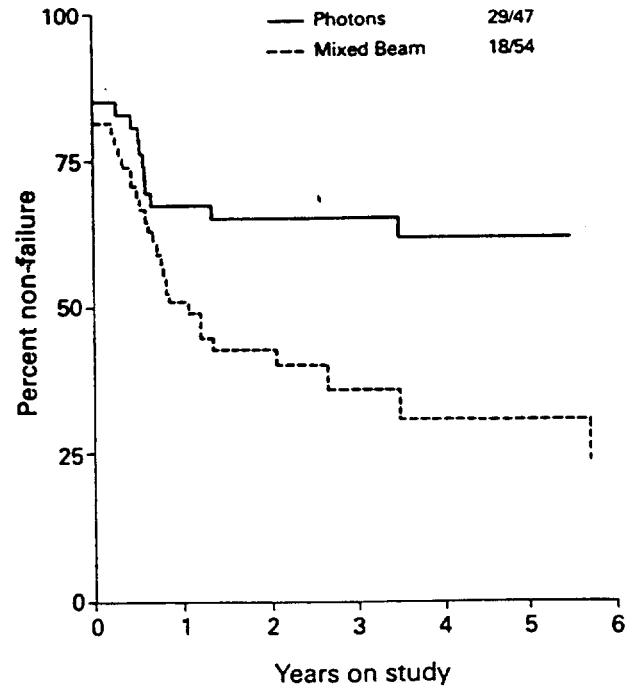

Fig. 4. Primary tumor control rates in patients presenting with negative lymph nodes as a function of treatment. The difference is significant at the $p = 0.006$ level.

rates for patients presenting with positive lymph nodes ($p = 0.55$). Figure 7 shows an advantage for photon-treated patients presenting with negative lymph nodes ($p = 0.01$).

Normal tissue toxicities were scored using the RTOG-EORTC scoring scale, and were more severe in mixed-beam-treated patients. The grade 3 or greater toxicity rate was 18% for mixed-beam-treated patients and 10% for photon-treated patients. This difference is statistically sig-

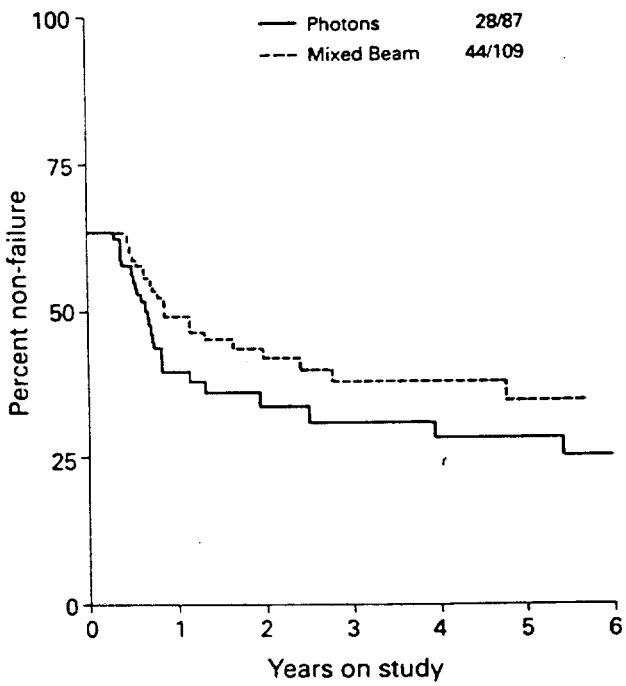

Fig. 3. Primary tumor control rates in patients presenting with positive lymph nodes as a function of treatment. The trend is not statistically significant ($p = 0.29$).

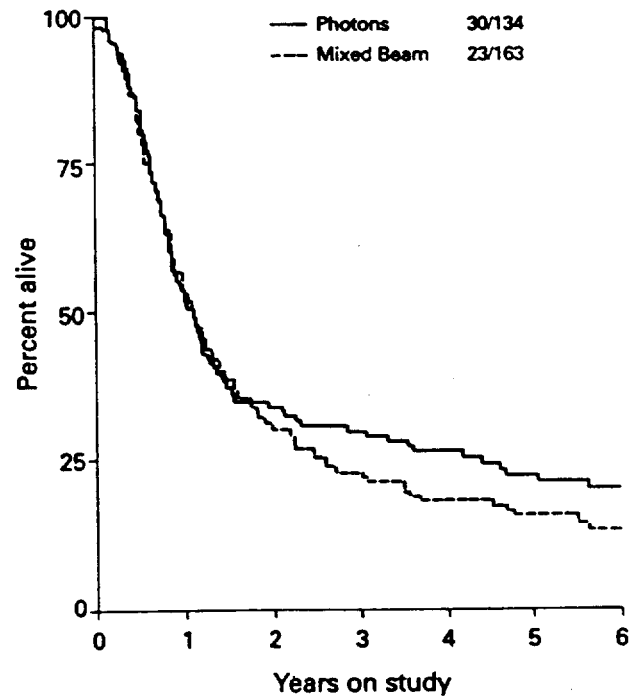

Fig. 5. Overall survival rates as a function of treatment. The difference is not statistically significant.

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Table 3. Cause of death

	Mixed beam		Photon	
	No.	(%)	No.	(%)
Loco-regional tumor	67	(42)	52	(39)
Distant metastases	25	(15)	15	(11)
New primary tumor	7	(4)	5	(4)
Radiotherapy complications	4	(2)	3	(2)
Chemotherapy complications	2	(1)	0	(0)
Surgical complications	3	(2)	2	(1)
Unrelated	27	(17)	21	(15)
Unknown	3	(2)	4	(3)
Not applicable (alive)	25	(15)	34	(24)

nificant at the $p = 0.02$ level. Table 4 lists normal tissue toxicities as a function of site. There are no significant differences in normal tissue toxicity rates comparing the primary sites to the nodal sites. There is no significant difference in incidence of second primary malignant tumors between the two treatment groups.

DISCUSSION

The use of fast neutron radiation therapy as a treatment for patients with advanced squamous cell carcinomas of the head and neck has been studied intermittently for 5 decades. The results of these investigations have been inconsistent. Following Stone's early work (11), Catterall *et al.* conducted a randomized study at the Hammersmith Hospital in London reporting a significant advantage for neutron radiation therapy over conventional photon treatment for patients with advanced squamous cell carcinomas of the head and neck (1). Using the low energy Medical Research Council (MRC) cyclotron, they observed a 76% (53/70) local control rate for neutrons compared to a 19% (12/63) local control rate for photons.

A second randomized trial was reported by Duncan *et al.* from the Western General Hospital at Edinburgh, which failed to confirm the results of Catterall *et al.* (3). One hundred and sixty-two patients were entered in this study. With a minimum follow-up period of 2 years, the local tumor control rate was 44.7% following neutrons and 45% following photons. The difference was not statistically significant.

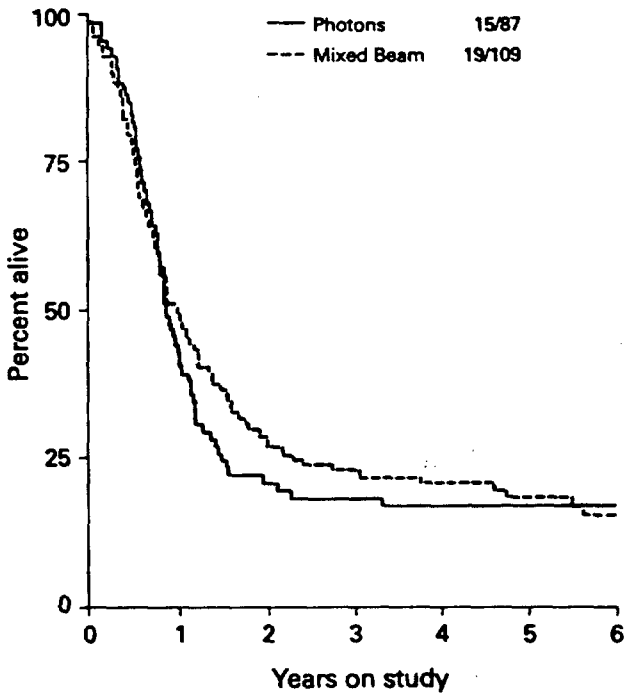

Fig. 6. Survival rates in patients presenting with positive lymph nodes as a function of treatment. The difference is not statistically significant.

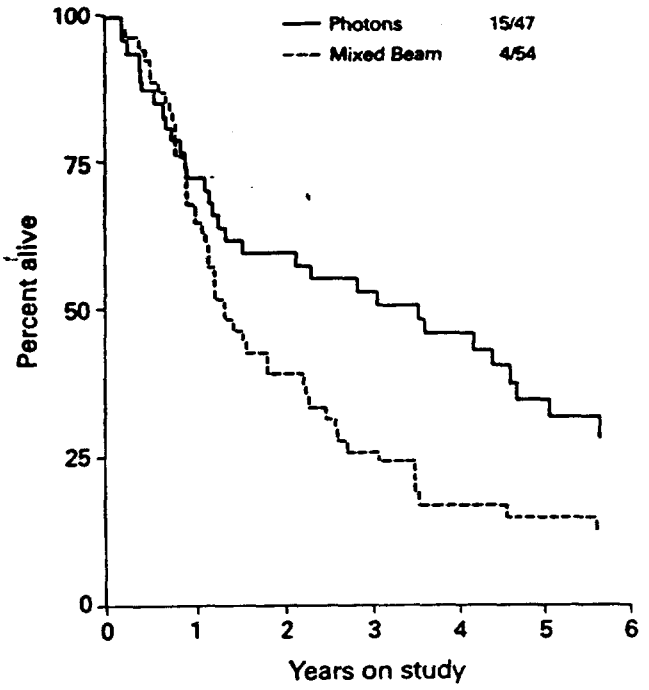

Fig. 7. Survival rates in patients presenting with negative lymph nodes as a function of treatment. The difference is significant at the $p = 0.01$ level.

Table 4. Normal tissue toxicity by treatment and site (Grade 3 or higher)

	Primary tumor site	Neck*
Fibrosis		
Mixed beam	4% (6/163)	8% (9/109)
Photons	2% (3/134)	5% (4/87)
Necrosis		
Mixed beam	12% (20/163)	4% (4/109)
Photons	7% (10/134)	1% (1/87)

* Node-positive patients receiving high dose treatment to the neck.

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The final results of the USA cooperative mixed beam study are now reported with a minimum follow-up period of 6 years. Although the overall results of this study fail to demonstrate a significant difference between the two treatment groups, subgroup analysis reveals major differences in results for patients presenting with positive lymph nodes versus those presenting with negative lymph nodes. The reasons for these differences are not readily apparent. With the large number of patients randomized and the low p values associated with the differences, random chance is not a probable explanation of these results. Both biological and physical explanations should be explored.

Guichard *et al.* were able to demonstrate that metastatic lymph nodes from an experimental mouse tumor contained an increased population of hypoxic cells when compared to equivalently-sized primary tumors (7). Since neutrons have a reduced OER when compared to photons and electrons, neutrons and other high LET treatments could be expected to achieve an improved result in such a tumor system with its increased population of hypoxic cells. However, if the differences between treatments observed in this study in patients presenting with positive and negative nodes were due to this effect, one would expect to see a consistency of response at the primary tumor site independent of nodal status, not the observed association of response between primary and nodal sites. Other studies have shown a reduced response to low LET radiations at the primary site in patients with squamous cell carcinomas of the head and neck presenting with positive lymph nodes (6). In a large retrospective analysis of the RTOG data base, lymph node positivity served as a predictor of response identifying tumors with biological characteristics leading to radioresistance to low LET radiations. These same characteristics potentially could make these tumors relatively more sensitive to high LET radiations. The incorporation of this type of selection criteria into clinical trials has been suggested by Withers (12). Although this hypothesis could explain the improved results observed in mixed-beam-treated patients presenting with positive nodes, it does not explain the unexpected finding of significantly improved results in photon-treated patients compared to neutron-treated patients presenting without positive lymph nodes. While a biological explanation is plausible and possible, it is not likely.

There are several possible explanations for the observed disparity of results between patients presenting with and without lymphadenopathy based on the physical distribution of radiation dose. The poor depth dose characteristics of the neutron beams available for this study would have resulted in an increased radiation dose to the neck compared to the deeper primary sites. In addition, the proportion of neutrons versus photons as a percentage of total dose would have been increased in the neck because of increasing gamma contamination of the neutron beams at depth. Although these physical characteristics of the neutron beams could explain an increased rate of nodal tumor control versus primary tumor control, they do not account for the differences in primary tumor control rates observed in patients presenting with and without positive lymph nodes. Underdosage of a portion of the primary tumors could have occurred as a consequence of the exaggerated "hour glass effect" associated with low energy neutron isodose curves at depth. Likewise, a geographic miss of a portion of the primary tumors could have occurred as a result of neutron treatment restrictions imposed by fixed horizontal treatment beams lacking adequate methods of port verification. In both instances, the larger field sizes required for patients presenting with positive nodes would have increased the chances of adequate coverage of the primary sites. Note that both primary tumor control and survival were worse in mixed-beam-treated patients presenting with negative nodes compared to mixed-beam-treated patients presenting with positive nodes, a finding inconsistent with the rest of the RTOG data base. The overall picture is consistent with "missing" some primary tumor in the node negative, mixed beam patients, and it would seem a combination of the last two factors presented would offer the most plausible explanation of the results observed in this study.

At the present time, an international consortium is conducting yet another study of fast neutron radiation therapy in advanced squamous cell carcinomas of the head and neck. With the introduction of high energy, hospital-based, isocentric cyclotrons the dose distribution and patient set-up limitations associated with the clinical trial reported in this paper will not be a factor in the new study. Likewise, the dose distribution properties of these new beams obviate the need for mixed beam treatment. Based on current accrual rates, the new study is projected to be completed in the early 1990's. Neutrons delivered in 12 fractions over 4 weeks are compared with standard photon/electron treatment. It is hoped that this study will provide a definitive answer to the 5-decade-old research question asking whether or not high LET treatment can offer a significant advance in the treatment of squamous cell carcinomas of the head and neck.

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