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Int. J. Radiation Oncology Biol. Phys., Vol. 10, pp. 2217–2221
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Pub. # 5008
Study # 7610
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Modality: part
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FAST NEUTRON RADIATION THERAPY FOR UNRESECTABLE SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK: THE RESULTS OF A RANDOMIZED RTOG STUDY

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Forty patients with advanced, unresectable squamous cell carcinomas of the head and neck were entered on a prospective, randomized study comparing fast neutron radiation therapy with conventional photon radiation therapy. Twenty-six patients were randomized to neutrons, and 14 patients were randomized to photons. The randomization was purposefully unbalanced in favor of the experimental treatment. The complete response rate for the neutron-treated group of patients was 52%. The complete response rate for the photon-treated group of patients was 17%. The difference is statistically significant at the $p = .04$ level. The two-year survival rates for the neutron-treated group and the photon-treated group were 25 and 0%, respectively. The major complication rates were not statistically significantly different for the two groups (18% for neutrons, and 33% for photons).

Head and neck cancer, Neutrons, High LET.

INTRODUCTION

An RTOG study was designed in 1977 to test the efficacy of neutrons used both alone and in a "mixed beam" treatment regimen vs. standard photon radiation therapy in patients with advanced, inoperable squamous cell carcinomas of the head and neck. The study was prospective and randomized: 40 patients were accrued to the photon vs. neutron randomization over a period of 63 months. The study was opened to patient accrual after the various independent neutron treatment centers in the United States joined together to conduct coordinated clinical research into the use of fast neutron beam radiation therapy.

Interest in fast neutron radiotherapy dates back to the 1940's when Stone used a neutron beam from an early physics cyclotron to treat patients with various advanced malignancies.[10] Almost all of his long-term survivors had severe radiation sequelae, leading him to the conclusion that these results were due to an increased relative biological effectiveness (RBE) for late effects compared to acute effects. This conclusion deterred further clinical investigation of fast neutron radiation therapy for approximately 20 years.

In the 1950's mammalian cell culture techniques were developed, and it became apparent that the shapes of post-irradiation cell survival curves were very different for high energy photons and fast neutrons. This meant that the RBE's for the treatment regimens used in Stone's clinical trials were much larger than those he extrapolated from large-dose-per-fraction preclinical animal model studies. Hence, much of the morbidity associated with the first clinical trials of fast neutrons could be attributed to inadvertently delivering extremely high radiation doses, as reflected by calculated nominal standard doses (Ellis NSD formula) of up to 3200 ret.[1]

Following Stone's early work, clinical trials were first resumed at Hammersmith Hospital, London, England, in the 1960's. After several hundred patients with extensive cancers were treated, it was concluded that fast neutron radiotherapy was well tolerated and that many advanced malignancies responded amazingly well.[2] Based on these very optimistic results, various centers throughout the world began clinical work with fast neutrons.

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Accepted for publication 16 July 1984.

alent to 2.5 Gy photon irradiation four times per week. The uninvolved neck and supraclavicular regions received the equivalent of 46–50 Gy photon irradiation in neutrons. The total treatment was delivered over an elapsed time of 7–8 weeks.

Patients with residual or recurrent disease at the primary site 90 to 120 days after treatment were to receive radical surgical treatment if feasible.

Thirty-five of the 40 patients randomized on the study are eligible for analysis. Three were ineligible and two were cancelled before the initiation of treatment. The reasons for ineligibility were: one patient was initially a surgical candidate (he was, in fact, treated surgically); one patient had prior radical surgery; and one patient had inadequate documentation of eligibility (no initial evaluation form submitted). Follow-up data were available on the remaining 35 patients (Table 2). Table 3 shows the on-study characteristics of the analyzable cases. Based on exact tests, none of the imbalances seen between the two groups are statistically significant.

Follow-up examinations were reported at three-month intervals for two years, at six-month intervals for the subsequent three years and then annually. The radiotherapy treatment plans, simulation films and port films were reviewed by a panel of radiation oncologists. All relevant data for each patient were reviewed at the RTOG statistical center and verified by the study chairman. Because of the small number of patients and the large number of strata, stratified analyses are not practical. Therefore, all analyses of data in this paper are unstratified. Survival comparisons will be made using the Mantel-Haenszel test, and survival curves and rates are calculated using the life table method of Kaplan and Meier.[8,9] All p-values reported are one-sided.

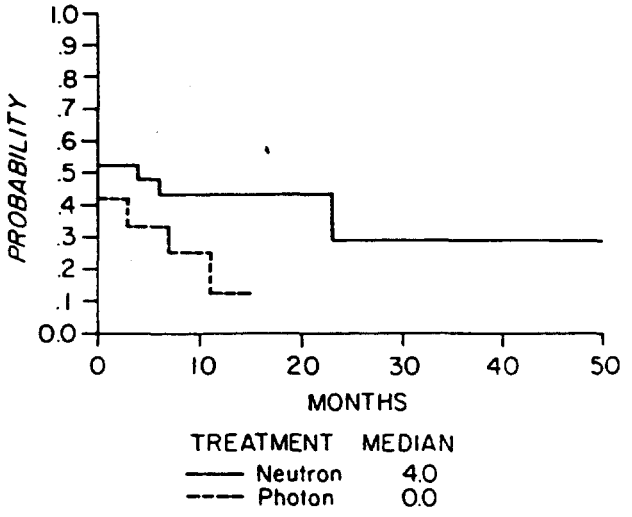

Fig. 2. Life table plot showing the probability of local/regional tumor control after attempted surgical salvage of primary treatment failures. The patients are divided according to treatment randomization. There were no surgical salvage procedures attempted in the neutron treatment group.

RESULTS

The local/regional control rates for the two treatment groups are displayed in Figure 1. All time measurements are computed from the date of randomization, and time to regional failure is defined as the interval prior to failure in the irradiated volume. This interval is considered zero for patients who never clear their disease. Complete remission induced by radiotherapy alone was observed in 52% of the neutron-treated patients and in 17% of the photon-treated patients. This difference is significant at the $p = .04$ level (exact test).

Figure 2 plots the local/regional control rates with surgical salvage. Complete remission rates with surgical

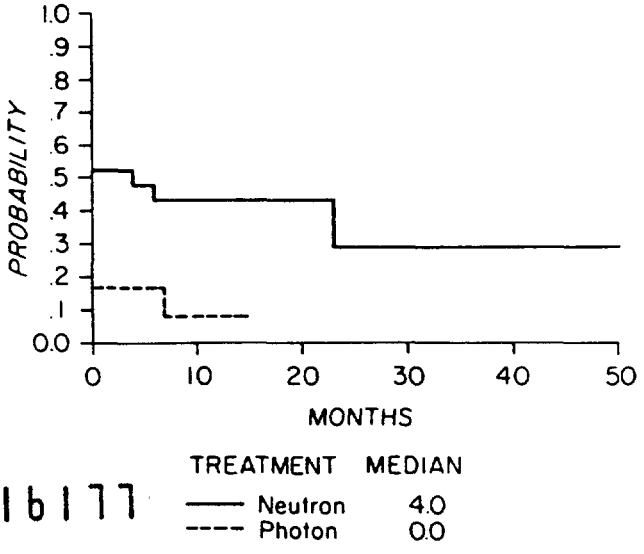

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Fig. 1. Life table plot showing the probability of local/regional tumor control by treatment randomization.

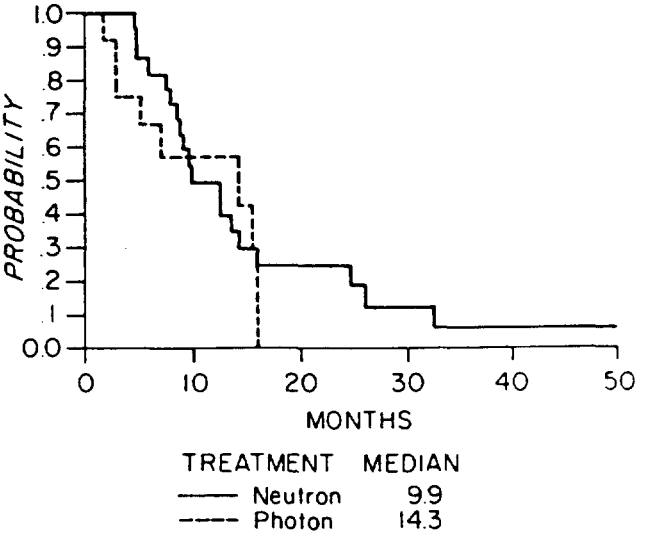

Fig. 3. Life table plot showing the probability of survival by treatment randomization.

cancer. Catterall *et al.* delivered their neutron dose in 12 fractions over 4 weeks with a low energy cyclotron.[2] Duncan *et al.* delivered the neutron irradiation in 20 fractions with a machine of equivalent energy.[6] The RTOG mixed beam study mixed neutrons with photons, and the RTOG neutron-only study delivered the neutron irradiation over 7 weeks with high energy machines (U.S. neutron treatment centers with low energy cyclotrons did not participate in the neutron-only randomization).[7]

The patient populations were distinctly different in the four reported studies as evidenced by the differences in photon local control rates (40% for Edinburgh, 25% for the RTOG mixed beam study, 19% for Hammersmith and 8% for the RTOG neutron-only study). The percent of patients with neck node involvement was also different (83% for the RTOG neutron-only study, 66% in the Hammersmith study, 66% in the RTOG mixed beam study, and approximately 50% in the Edinburgh study).[2,6,7]

One possible explanation for the advantage demonstrated in this study for neutrons over photons is the possibility of an inordinately poor result in the photon control arm. In order to better evaluate the results of this work, comparisons were made between the neutron-treated group of patients in this study and patients from the RTOG mixed beam vs. photon study.

Table 4 lists the factors predictive for survival in the RTOG neutron and mixed beam studies (stepwise Cox model).[4] The group of patients randomized to the neutron vs. photon study were significantly more advanced than the group of patients randomized to the mixed beam vs. photon study. For each prognostic factor, the neutron group had a smaller proportion with favorable prognosis.

Figure 5 compares the survival curves for photons, neutrons, and mixed beam irradiation corrected for the prognostic factors listed in Table 4.[3] The survival advantage for neutrons is significant at the $p = .04$ level. Using this method of analysis, there is a 37% improvement in survival at 5 years for this group of advanced patients treated with neutrons over comparable groups of patients treated with photons or mixed beam irradiation.

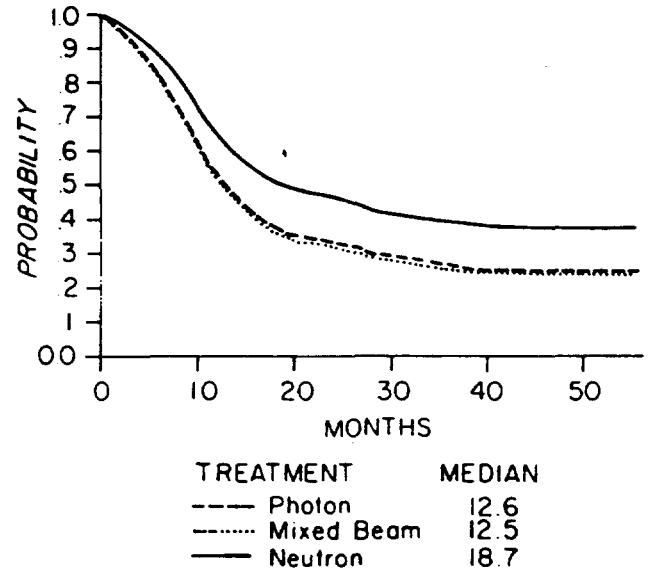

Fig. 5. Life table plot showing the prognostic-factor-corrected survival rates comparing patients treated with photons, neutrons and mixed beam irradiation in the RTOG Phase III neutron studies.

The results of this study demonstrate a possible advantage for neutrons when compared to photon radiation therapy in a group of patients with very advanced squamous cell carcinomas of the head and neck. The improved local control and survival rates are attended by a favorable complication rate (18 vs. 33%). Future studies using the new hospital-based high energy cyclotrons currently coming into service in the U.S. may lead to further improvements in complication-free survival for patients with squamous cell carcinomas of the head and neck. If larger studies using these new higher energy cyclotrons confirm the results of this study, it will be time to move fast neutron radiation therapy into the private medical sector.

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