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● *Clinical Original Contribution*

NEUTRON VERSUS PHOTON IRRADIATION FOR UNRESECTABLE SALIVARY GLAND TUMORS: FINAL REPORT OF AN RTOG-MRC RANDOMIZED CLINICAL TRIAL

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Purpose: To compare the efficacy of fast neutron radiotherapy versus conventional photon and/or electron radiotherapy for unresectable, malignant salivary gland tumors a randomized clinical trial comparing was sponsored by the Radiation Therapy Oncology Group in the United States and the Medical Research Council in Great Britain.
Methods and Materials: Eligibility criteria included either inoperable primary or recurrent major or minor salivary gland tumors. Patients were stratified by surgical status (primary vs. recurrent), tumor size (less than or greater than 5 cm), and histology (squamous or malignant mixed versus other). After a total of 32 patients were entered onto this study, it appeared that the group receiving fast neutron radiotherapy had a significantly improved local/regional control rate and also a borderline improvement in survival and the study was stopped earlier than planned for ethical reasons. Twenty-five patients were study-eligible and analyzable.
Results: Ten-year follow-up data for this study is presented. On an actuarial basis, there continues to be a statistically-significant improvement in local/regional control for the neutron group (56% vs. 17%, $p = 0.009$) but there is no improvement in overall survival (15% vs. 25%, p = n.s.). Patterns of failure are analyzed and it is shown that distant metastases account for the majority of failures on the neutron arm and local/regional failures account for the majority of failures on the photon arm. Long-term, treatment-related morbidity is analyzed and while the incidence of morbidity graded "severe" was greater on the neutron arm, there was no significant difference in "life-threatening" complications. This work is placed in the context of other series of malignant salivary gland tumors treated with definitive radiotherapy.
Conclusions: Fast neutron radiotherapy appears to be the treatment-of-choice for patients with inoperable primary or recurrent malignant salivary gland tumors.

Salivary gland malignancies, Fast neutron radiotherapy.

INTRODUCTION

Primary malignant tumors of the major and minor salivary glands are relatively rare entities constituting only about 3–5% of all head and neck malignancies. They also represent a diverse group of histologies (12, 17) and so most clinical series tend to be small and contain tumors with disparate behaviors in terms of aggressiveness and patterns of spread. Hence, it can be difficult to make generalizations from the published literature. Historically, salivary gland tumors were thought to be "radioresistant" but today the role of radiotherapy as a postoperative adjunct to surgery has become well recognized. Unfortunately, the use of conventional radiotherapy alone for patients with unresectable lesions is less successful with overall local control rates averaging about 26% (3, 6, 9, 10, 11, 13, 15, 23, 24, 25, 27, 29, 33).

Given the relatively poor results with conventional low linear energy transfer (LET) radiotherapy and the superficial location of the tumors, salivary gland malignancies

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were a natural tumor system for early neutron studies. The first radiobiological evidence that neutrons offered a major therapeutic advantage is attributed to Batterman *et al.* (1) who measured the relative biological effectiveness (RBE) of fast neutrons relative to megavoltage photons for human tumors metastatic to lung. Using growth delay as an endpoint, they found the highest RBE occurred for adenoidcystic carcinoma from a salivary gland primary. The RBE for fractionated radiotherapy was found to be 8.0 compared to 3.0–3.5 for most normal tissues. To put this in perspective, if one were to give a dose of 2,000 neutron cGy to a parotid tumor, the biological effect in terms of the mucosa and temporomandibular joint would be equivalent to 6,000–7,000 photon cGy but the biological effect on the tumor would be equivalent to 16,000 photon cGy—a therapeutic gain factor of 2.3–2.6. For a detailed discussion of the differences between the radiobiological properties between neutron and photon radiation, the reader is referred to the text by Hall (16).

Many nonrandomized neutron clinical trials seemed to support this conclusion (2, 5, 7, 8, 21, 22, 26, 28). Based upon the earlier of these reported series, the Radiation Therapy Oncology Group (RTOG) in the United States and the Medical Research Council (MRC) in Great Britain launched a Phase III, randomized clinical trial (80-01) to compare fast neutron radiotherapy vs. conventional photon irradiation for patients with unresectable salivary gland tumors. The fast neutron group achieved significantly improved tumor clearance at both the primary site and in the regional lymph nodes. At the 2-year endpoint the local/regional control rates were 67% for the neutron group compared to 17% for the photon group ($p < 0.005$) and survivals were 62% for the neutron group compared to 25% for the photon group ($p = 0.1$) based upon one-sided logrank testing (14). Moreover, the initial clearance rates of involved lymph nodes was 86% in the neutron group compared to 25% in the photon group. Although only 32 patients had been entered onto this study with only 25 being eligible and evaluable, the participating neutron treatment facilities became increasing reluctant to continue the study given these dramatic differences. Hence, the study was closed early for ethical reasons. This study has recently been updated and the purpose of this paper is to report the long-term results both for treatment efficacy and treatment-related complications.

METHODS AND MATERIALS

In the interests of efficiently using journal space, we will only briefly review the protocol criteria and treatment procedure here. For a more detailed description of these as well as the review methodology, the reader is referred to the initial publication by Griffin *et al.* (14).

To be eligible for this study patients had to have either inoperable or unresectable primary or recurrent malignant tumors of the major or minor salivary glands. The following histologies were eligible: mucoepidermoid carcinoma, acinic cell carcinoma, adenoidcystic carcinoma, adenocarcinoma, squamous cell carcinoma, and malignant mixed tumors. Patients also had to have been between 18–76 years of age, had no history of other prior malignancies (other than nonmelanoma skin cancer), had not received prior radiation therapy, and had to have a Karnofsky performance status of ≥ 60. Patients were randomized to receive either conventional megavoltage photon/electron irradiation or fast neutron irradiation. Informed consent was given by all patients who entered the study.

Four institutions participated in the study: Fermi Laboratory; Edinburgh, Scotland; University of Pennsylvania; and the University of Washington. The neutron beams from these four facilities were different and their relative biological effectiveness (RBE) varied accordingly. While the neutron irradiation was always given in 12 fractions over a 4-week period, the overall total dose was scaled according to the RBE's of the individual facility: 22 $Gy_{n\gamma}$ for the Fermi Laboratory facility, 17.14 $Gy_{n\gamma}$ for the University of Pennsylvania facility, 16.5 $Gy_{n\gamma}$ for the Edinburgh facility, 17 $Gy_{n\gamma}$ for the original University of Washington facility, and 20 $Gy_{n\gamma}$ for the new hospital-based University of Washington cyclotron facility. Patients randomized to the photon/electron control arm received 70 Gy in 7.5 weeks on the U.S. facilities and 55 Gy in 4 weeks at the Edinburgh facilities. These control patients were treated once-a-day, 5 days per week with the two different treatment regimens reflecting the standard definitive radiotherapeutic treatments used in the United States and the United Kingdom at the time the study was carried out. These were thought to be clinically-equivalent in regards to treatment efficacy.

Patients were stratified by surgical status (inoperable primary tumors vs. recurrent unresectable tumors), tumor size (> 5 cm vs. < 5 cm), and histology (squamous or malignant mixed vs. other). The study was opened in July, 1980 and closed in March, 1986 after accruing 32 patients. Two patients randomized to the photon/electron control arm and one patient randomized to fast neutron radiotherapy were subsequently found to be ineligible because they had only microscopic (i.e., nonmeasurable) disease at the time of randomization, one patient who was randomized to the photon/electron control arm refused all treatment, and three other patients were ineligible for various reasons: 1 had a benign tumor histology, 1 had a mucosal carcinoma not of salivary gland origin, and 1 had a prior rectal carcinoma. There were hence 12 patients on the photon/electron control arm and 13 patients on the neutron arm who were both eligible and evaluable. The pretreatment characteristics of these patients and the details of the protocol quality control are summarized in the original report by Griffin *et al.* (14). Although the number of evaluable patients was small, as noted above there was a statistically-significant difference in local/regional control at 2 years and there was a suggestive dif-

ference in survival. In addition, the results of several, nonrandomized series of patients treated with fast neutrons were becoming known which supported the results of the randomized trial and there was considerable reluctance on the part of the treating institutions to continue the study.

The last patient was entered onto this study in October, 1985. Hence, the minimum "time-at-risk" for the present analysis is 76 months. The time scale for outcome analysis is measured from the start of treatment until failure or the time of last follow-up if the patient did not fail. Differences in local/regional control are measured by two-sided Mantel-Haenszel logrank testing (20). The plots shown in the following section are step functions obtained using the Kaplan-Meier method (19). Chi-square testing is used to assess the significance of differences in complication rates.

RESULTS

Patients were considered to have complete clearance of their local/regional disease if both the primary tumor mass and any clinically-positive lymphadenopathy totally disappeared both clinically and radiographically. Patients who did not achieve a complete tumor clearance initially were considered as "failures" on study day one. Patients who achieved an initial complete tumor clearance were considered as a "failure" on the study day a recurrence was reported. With respect to survival, death was considered a "failure" regardless of the cause or whether or not active tumor was present at the time.

The probability of local/regional failure for the two treatment arms is shown in Figure 1. This plot is basically the complement of local/regional control with the starting values representing the initial local/regional failure rates. There have been nine failures on the photon arm compared to four failures on the neutron arm. On an actuarial basis, the 10-year local/regional control probability is 17% for the photon-treated patients compared to 56% for the neutron-treated patients. The difference between the two curves is statistically-significant at the $p = 0.009$ level.

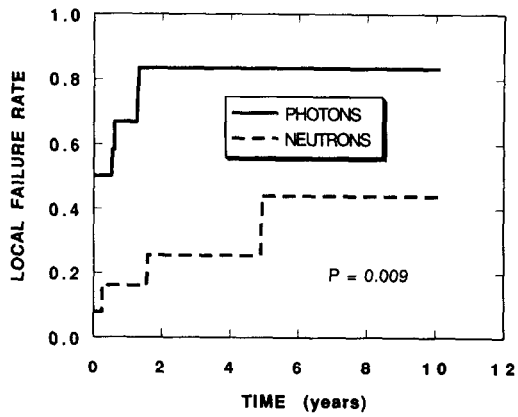

Fig. 1. Probability of local/regional failure for patients entered on the two treatment arms of the protocol. The photon arm is shown as the solid curve and the neutron arm is shown as the dashed curve. The starting values of the curves represent the initial local/regional failure rates. The difference between the two curves is statistically-significant at the $p = 0.009$ level.

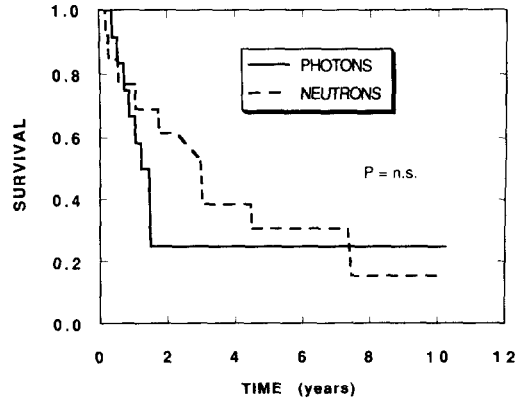

Fig. 2. Survival probabilities for the patients entered on the two treatment arms of the protocol. The photon arm is shown as the solid curve and the neutron arm is shown as the dashed curve. There is no statistically-significant difference between the two curves ($p = 0.50$).

Survival probabilities for the two treatment groups are shown in Figure 2. There have been 9 deaths on the photon arm and 10 deaths on the neutron arm. On an actuarial basis, the 10-year survival is 25% for the photon-treated patients compared to 15% for the neutron-treated patients. There is no statistically-significant difference between the two curves ($p = 0.50$).

The failure of improved local/regional control to favorably impact survival may be explained in terms of the metastatic spread of the tumors. Seven patients on the photon arm developed distant metastases—four with an associated local recurrence and three with solely distant metastases. Nine patients on the neutron arm developed distant metastases—four with an associated local recurrence and five with solely distant metastases. The longer median survival of the neutron-treated group (2.97 years vs. 1.23 years) may have allowed for the development of distant metastases in patients that otherwise would have succumbed to local/regional disease. Figure 3 shows the distant metastases failure rate for the two arms calculated on an actuarial basis to correct for the decreasing number of patients at risk for the longer follow-up times. Note that for times shorter than 2 years, the rates are the same on the two arms in keeping with the survival rates being essentially the same for these shorter times. It is only for the longer follow-up times that the higher incidence of distant metastases is manefest on the neutron arm and this is consistent with the reduced death rate from local failures.

Treatment related morbidity was assessed using the joint RTOG/EORTC scoring schema. Acute and intermediate time frame morbidity has already been reported in the initial report by Griffin *et al.* (14) and so here we will emphasize late effects. Ten patients on the photon

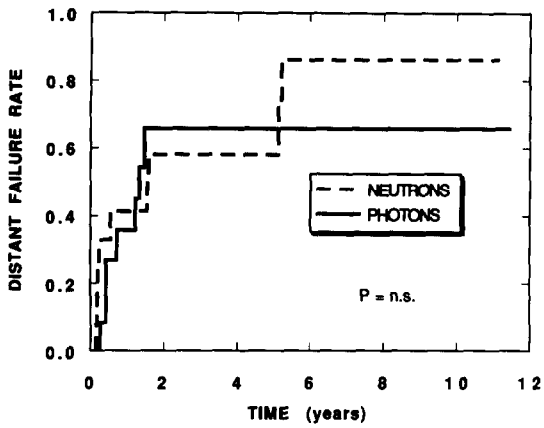

Fig. 3. Probability of distant failure for patients entered on the two treatment arms of the protocol. The photon arm is shown as the solid curve and the neutron arm is shown as the dashed curve. There is no statistically-significant difference between the two curves ($p = 0.79$).

arm and all 13 patients on the neutron arm experienced some degree of morbidity. Table 1 summarizes those reactions graded "severe or greater" according to the type of complication and treatment arm. Nine patients on the neutron arm had at least one such complication compared with four patients on the photon arm ($p = 0.07$). There were two patients with "life-threatening" complications on the neutron arm compared to one patient with a "life-threatening" complication on the photon arm; there were no fatal complications on either arm. While the morbidity associated with the neutron treatment was somewhat greater than that associated with the photon treatment, it did not detract appreciably from its clinical utility in achieving a better local/regional control rate.

DISCUSSION

The use of fast neutron radiotherapy in the treatment of human malignancies dates back to the early work of Stone and co-workers in the 1930's (30). Since then, there has been considerable clinical and laboratory work done in order to delineate the role of this modality in the treatment of cancer. Neutrons have not proven to be a panacea for all the tumor systems upon which they have been tested, but salivary gland malignancies have consistently stood out as a system where the results have been better than would have been expected with conventional radiotherapy. Tables 2 and 3 provide, respectively, summaries of the local control results for patients with inoperable tumors treated definitively with conventional photon/electron irradiation and fast neutron irradiation. These are not randomized trials and span a relatively long time period with follow-up times varying considerably from series to series. Moreover, they represent a spectrum of different tumor stages and histologies. However, in aggregate they represent a large body of data showing a local control rate of 26% (78/298) for patients treated with conventional photon irradiation compared to 67% (208/309) for patients treated with fast neutron radiotherapy and

Table 1. Treatment related complications graded "severe or greater" according to the joint RTOG/EOTRC scoring schema

	Photons	Neutrons
Hoarseness	0	1
Dysphagia	1	2
Dehydration	1	2
Malnutrition	1	2
Pain	0	3
Mucosal	1	3
Skin	2	2
Fibrosis	1	2
Necrosis	0	3
Xerostomia	2	1
Impaired taste	1	4
Other	0	1

Note: Some patients exhibited more than one type of complication. There were no fatal complications on either treatment arm.

Table 2. Local/regional tumor control rates for malignant salivary gland tumors using low LET (photon/electron) radiotherapy in conventional fractionation schemas from nonrandomized studies

	Patient number	Control rate %	(No.)
Fitzpatrick and Thoriault (11)	50	12	(6/50)
Vikram *et al.* (33)	49	4	(2/49)
Borthne *et al.* (3)	35	23	(8/35)
Rafla (23)	25	36	(9/25)
Fu *et al.* (13)	19	32	(6/19)
Stewart *et al.* (29)	19	47	(9/19)
Ellis *et al.* (10)	17	29	(5/17)
Dobrowsky *et al.* (6)	17	41	(7/17)
Shidnia *et al.* (27)	16	38	(6/16)
Guillamondi *et al.* (15)	15	60	(9/15)
Elkon *et al.* (9)	13	15	(2/13)
Ravasz *et al.* (24)	12	25	(3/12)
Rossman (25)	11	54	(6/11)
Overall	298	26	(78/298)

Table 3. Local/regional tumor control rates for malignant salivary gland tumors using high LET fast neutron radiotherapy from nonrandomized studies

	Patient number	Control rate %	(No.)
Saroja *et al.* (26)	113	63	(71/113)
Catterall and Errington (5)	65	77	(50/65)
Buchholz *et al.* (4)	52	77	(40/52)
Batterman and Mijnheer (2)	32	66	(21/32)
Duncan *et al.* (7)	22	55	(12/22)
Maor *et al.* (21)	9	67	(6/9)
Ornitz *et al.* (22)	8	38	(3/8)
Eichhorn *et al.* (8)	5	60	(3/5)
Skolyszewski *et al.* (28)	3	67	(2/3)
Overall	309	67	(208/309)

there is a fairly consistent picture exhibited by the entries in these tables. The earlier studies in both tables share the common feature that the patients were treated with more primitive equipment than is available today.

To provide a more definitive test of the efficacy of this modality compared to conventional photon/electron irradiation, the RTOG in the United States and the MRC in Great Britain conducted a randomized clinical trial. Patient accrual to this study was slow and as it progressed and more information was published regarding the relative efficacy of fast neutron irradiation, there was a great reluctance on the part of the treating institutions to continue it. An initial report was published on the 2-year follow-up data which showed a statistically-significant improvement in local/regional control and a marginal improvement in survival (14). Herein we have presented a final report on the long-term results for the major endpoints of the study.

We continue to find a statistically-significant increase in 10-year local/regional control rates with fast neutrons—56% vs. 17% ($p = 0.009$)—but no difference in survival rates—15% vs. 25% (p = n.s.). The survival curves do appear to separate for follow-up times between 1 and 4 years bearing out the findings in the initial report (14). Analysis of the pattern-of-failure shows that there was an extremely high rate of distant metastases in each arm—7/12 patients on the photon arm and 9/13 patients on the neutron arm—which may account for the failure of improved local/regional control to be translated into improved survival. The development of distant metastases was essentially the same in each arm for the earlier follow-up times reflecting the advanced nature of the tumors treated in this study. Clearly, local/regional control is only part of the problem in the treatment of patients with advanced salivary gland tumors but unfortunately, chemotherapeutic regimens for this disease are currently suboptimal (18, 31, 32).

The issue of long-term morbidity was addressed and while the incidence of treatment related complications was greater on the neutron arm, the degree of these complications was not such as to argue against the use of fast neutrons in this clinical setting. It should also be noted that the majority of these patients were treated using low-energy neutron beams from relatively unsophisticated treatment facilities originally designed for physics research purposes. Currently, the majority of neutron treatment facilities use high energy beams generated in technically-sophisticated, hospital-based treatment facilities. The treatment morbidity associated with such units is much less than with the older units.

A recent report indicates that the results of conventional photon irradiation may be improved by using an accelerated radiation fractionation schema. The photon series summarized in Table 2 all used a once-a-day conventional fractionation schema and a report by Wang and Goodman (34) using a BID fractionation schema shows 5-year actuarial local control rates of 100% for 9 parotid tumors and 78% for 15 minor salivary gland tumors. These patient numbers are small and their series is nonrandomized so further confirmatory work is needed.

We feel that at present the overall clinical picture indicates that fast neutron radiotherapy is the "treatment-of-choice" for patients with unresectable lesions. Recent work shows its efficacy in the postoperative treatment of certain patients at high risk for local/regional recurrence (4). This latter work also argues against the necessity for extensive surgery if the attendant morbidity (i.e., damage to facial nerve) is too great.

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