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● Editorial

FAST NEUTRON RADIOTHERAPY FOR INOPERABLE SALIVARY GLAND TUMORS: IS IT THE TREATMENT OF CHOICE?

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Salivary gland tumors are relatively rare, comprising approximately 1-3% of all head and neck malignancies. They can arise in a variety of different sites (e.g., parotid gland, submandibular gland, sublingual gland, minor salivary glands) and consist of diverse histologies having varying potential for aggressive local behavior and distant spread. Reported series thus tend to be small and difficult to compare with each other. Moreover, the series tend to cover many years of treatment with changes both in treatment equipment and technique occurring over the time span in question. With these constraints, it is understandable why the role of radiotherapy for malignant tumors of the salivary gland is still in an unsettled state.

Classically these tumors have been considered as "radioresistant" and surgery has been the primary treatment modality. Subsequently a review of the literature by Reddy *et al.*¹⁴ showed that postoperative radiotherapy could appreciably reduce the local recurrence rates in patients having a high risk of microscopic residual disease. The situation is not so favorable for inoperable tumors or for tumors recurrent after an initial surgical resection. The situation for low linear energy transfer (LET) photon or electron irradiation alone is summarized in Table 1 which represents a fairly extensive review of the literature. Patients treated postoperatively for microscopic residual disease or in a palliative manner with low doses of radiation are not included in the table. The long term local control rate based upon a total of 188 patients is only 28%. Note that the often quoted work by King and Fletcher¹⁰ showing an 81% local control rate is not included in Table 1 because in reality it considers mostly patients treated postoperatively for microscopic residual disease.

Given the combination of a relatively poor outlook with conventional treatment and the superficial location of the tumors, salivary gland malignancies were a natural tumor system for early neutron radiotherapy studies.

The initial work was largely done using neutron generators built primarily for physics research purposes and subsequently adapted to medical use. They were primitive and their beams often had penetrating properties more like old-fashioned, orthovoltage units than modern megavoltage linear accelerators or ⁶⁰Co units. Nevertheless, while there is still considerable controversy in the efficacy of fast neutrons for the treatment of most malignancies, there is nearly unanimous agreement that for salivary gland tumors, the results are much better than could be obtained with conventional radiotherapy.

The first radiobiological evidence that neutrons should be particularly effective in the treatment of salivary gland tumors is due to Batterman *et al.*¹ who measured the relative biological effectiveness (RBE) relative to ⁶⁰Co radiation for neutrons produced by d → T reactions using human tumors metastatic to lung. They determined the RBE for growth delay in terms of the time required for tumor mass to return to its pre-irradiation volume as evaluated on serial radiographs. Patients having two or more metastases had lesions simultaneously treated with the two types of radiation. A wide range of RBE's was found but an adenoidcystic carcinoma from a parotid gland primary was found to be among the highest: RBE = 5.7 for a single radiation dose and RBE = 8.0 for multiple radiation fractions such as would correspond to clinical treatment schemes. For most other tumors, the RBE's were in the range of 2.5-4.0.

Clinical results overwhelmingly support this conclusion. The local control rates for salivary gland tumors treated with fast neutrons are summarized in Table 2. The Fermi laboratory work reported by Saroja *et al.*,¹⁵ in this issue, is the largest single series to date. It comprises 113 evaluable patients with gross tumors treated with fast neutron radiotherapy between September 1976 and December 1984. Ten patients were re-irradiated for a recurrence in a region that had already received postoperative low LET radiotherapy. The local control rate as 67% for

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Table 1. Summary of local control rates for malignant salivary gland tumors treated with photon and/or electron beam irradiation and/or radioactive implants

	Number of patients	Local control
Borthne <i>et al.</i> ³	35	8/35 (23%)
Fitzpatrick and Theriault ⁷	50	6/50 (12%)
Fu <i>et al.</i> ⁸	19	6/19 (32%)
Shidnia <i>et al.</i> ¹⁶	16	6/16 (38%)
Elkon <i>et al.</i> ⁶	13	2/13 (15%)
Rossmann ¹⁴	11	6/11 (54%)
Raffa ¹³	25	9/25 (36%)
Stewart <i>et al.</i> ¹⁸	19	9/19 (47%)
Overall	118	52/188 (28%)

Note: Patients treated de novo and for gross disease after a post-surgical recurrence are included but not patients who were treated postoperatively for microscopic residual disease.

tumors of the major salivary glands and 58% for tumors of the minor salivary glands for an overall value of 63%. For tumors less than 5 cm in diameter, the local control rate was 74%—a value as high as that expected for a complete excision followed by postoperative photon irradiation for more accessible lesions. They noted that all histologies responded equally well to the neutron treatments. Although the overall complication rate was 23%, it dropped to 16% for patients receiving less than 24 Gy_n. Currently 20 Gy_n is thought sufficient to maintain excellent control rates for these tumors. This lower dose should reduce the morbidity even further and certainly to a level that is much less than that caused by an uncontrolled malignancy. In no instance was there any damage of the facial nerve by the neutron beam.

These conclusions are supported by all of the other reported neutron series shown in Table 2. Based upon 267 patients, the overall local control rate is 68%—more than twice as great as the overall low LET radiation experience.

To verify the above experience in the context of a controlled clinical trial the EORTC and the RTOG jointly

Table 2. Summary of local control rates for malignancy salivary gland tumors treated with neutron irradiation

Facility	Number of patients	Local control
Fermi ¹⁵	113	71/113 (63%)
Hammersmith ⁴	65	50/65 (77%)
Mantq ¹²	8	3/8 (38%)
Amsterdam ²	32	21/32 (66%)
Tamvec ¹¹	9	6/9 (67%)
CICR ⁵	5	3/5 (60%)
Krakow ¹⁷	3	2/3 (67%)
U. Washington	32	26/32 (81%)
Overall	267	182/267 (68%)

Note: Patients treated de novo and for gross disease after a post-surgical recurrence are included but not patients who were treated postoperatively for microscopic residual disease. Ten patients in the FERMI series, 14 patients in the HAMMER-SMITH series and 4 patients in the AMSTERDAM series had received prior photon or electron beam radiotherapy and were retreated with neutrons after a documented failure.

sponsored a study for inoperable salivary gland lesions.⁹ The results were so overwhelmingly in favor of the neutron arm that the study was closed early. Based upon 25 evaluable patients, the initial complete response rate at the primary site for the neutron arm was 85% compared with 33% for the photon arm. The complete tumor clearance rate in clinically-positive cervical neck nodes was 67% for neutrons and 0% for photons. With a minimum follow-up time of 1 year, the overall local/regional control rate was 53% for the neutron arm and 31% on the photon arm. The actuarial survival at 2 years was 55% for the neutron group and 13% for the photon group.

If anything, the sophisticated, hospital-based, neutron therapy centers that have recently been activated in the United States, England, and Korea, should further improve the local control rates for these tumors. Placed in the context of the information shown in Tables 1 and 2, I believe that one can indeed conclude that fast neutron radiotherapy is the present "treatment of choice" for inoperable malignant tumors of the salivary glands. Additional work may extend this conclusion to the smaller tumors currently treated primarily with surgery.

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