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FAST NEUTRONS IN THE TREATMENT OF SALIVARY GLAND TUMORS

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ABSTRACT

Fast neutrons were used in the management of thirty patients with advanced salivary gland tumors. Twenty-two patients are the subject of this analysis. In only seven patients neutrons were used as the primary mode of management. The remaining patients either had recurrent disease after surgery and/or radiation, or received post-operative treatment with neutrons. After a minimum follow-up of one year, 66% of the patients are NED. However, control in the treatment volume is as high as 77% suggesting a definite improvement in the treatment of advanced salivary gland tumors.

KEY WORDS Neutrons, Salivary Gland Tumors.

FAST NEUTRONS IN THE TREATMENT OF SALIVARY GLAND TUMORS

Neoplasms of the salivary gland constitute only 0.4% of all tumors and yet they continue to pose a difficult management problem. Their capricious clinical nature frustrates the surgeon and radiotherapist alike. Radical removal has proved unsatisfactory due to cosmetically unacceptable 7th nerve palsy. Subtotal resection with sparing of the nerve traversing the parotid gland has led to an increased rate of local persistence. One approach to increasing the rate of local control is the addition of radiation therapy either as a pre-operative or a post-operative measure.¹ However, the results have not been entirely satisfactory. Fast neutrons have been used in Hammersmith Hospital in London for recurrent and/or inoperable tumors, and the best results reported to date have been obtained.² A similar study was done at Fermilab (Chicago) which forms the basis of this report.

MATERIALS AND METHODS.

Fast neutron therapy was used for treatment of advanced carcinoma of salivary glands in 30 patients

treated at the Fermi National Accelerator Laboratory. These are a part of an ongoing Phase II study to determine the efficacy of neutrons in controlling the locally menacing problem posed by these tumors. After completion of treatment, these patients were requested to return to our facility every 4 to 8 weeks for a complete evaluation to assess the tumor response and determine any significant untoward effects from the treatment. Twenty two patients have been followed for a minimum of one year and are considered eligible for presentation in this analysis.

Patient Population.

Age: Patients' ages ranged from 24 years to 79 years with a median of 55 years.

Location: Neoplasms had originated in a major salivary gland in 17 patients and in only 5 cases in the minor salivary glands located in the hard palate, the buccal mucosa and floor of the mouth and base of tongue. Of the major salivary gland most occurred in the parotid gland.

Table I shows the distribution of tumors according to their site of origin.

Pathology: Most common histological types were encountered. Except for one massive "mixed" tumor, all were carcinomas.

Table II depicts the distribution of the patients according to the pathological subtypes suggested by Foote and Frazell.³

Previous Management.

Neutron therapy was the primary mode of management in 7 patients. Five more patients underwent surgery but had residual disease and therefore received post-operative neutron irradiation.

The remaining 10 patients had undergone multiple excisions for recurrent disease. Of these, 2 patients had previously received conventional irradiation in full tumoricidal doses.

Technique.

The neutrons are produced from a thin beryllium target using 66 MeV protons. The relative biologi-

cal effectiveness of this beam is approximately three. The skin sparing and depth dose characteristics are similar to 4 MeV x-rays.⁴ Due to the fixed horizontal neutron beam patients were treated in the sitting position with their heads immobilized with a "Lite-cast".

Treatment plans were individualized for each patient keeping in mind the anatomy of the gland and the behaviour of various pathological subtypes.

The first echelon of lymph node drainage was always included in the treatment volume. An attempt was made to spare the contralateral mouth and neck and to minimize the dose to the spinal cord. Fig. 1 depicts a typical treatment plan. This was accomplished by using a wedged pair, 24.0 Gy being delivered to the 90% isodose line. Not more than 12.5 Gy were delivered to the spinal cord (tolerance limit taken as 50 Gy photons) as the RBE for central nervous tissue is estimated to be 4.

When the initial wide-field irradiation was done with photons, the neck received 45.0 Gy with photons, followed by 7.5 Gy of neutrons as a boost to the gross disease only.

RESULTS.

Tolerance: Acute reactions including loss of taste, dryness of mouth, and erythema of the treated skin occurred as expected with conventional irradiation. Mucositis occurred less frequently and was not of a severe degree.

Response: Of 14 patients with gross disease treated with neutrons alone, all showed regression to some extent during the course of treatment. Complete regression of tumor occasionally took 3 to 4 months.

Follow-up in 7 patients who were treated primarily with neutrons ranged from 1 year to 3 years. Of these, only 1 tumor recurred in the target volume in 11 months after treatment. This patient also developed pulmonary metastasis. One other patient who had massive involvement of the parotid with destruction of the coronoid process and mandibular ramus and large lymph nodes in the neck measuring 6 x 5 cm, has developed metastatic lesions in the lung

parenchyma and also has disease outside the irradiated volume. The remaining 5 patients remain tumor free.

Of 3 patients who were treated post-operatively with neutrons, 1 failed in the treatment volume with persistent disease 3 months later. He died 7 months after finishing treatment. The remaining 2 have remained free of disease 2 years post treatment.

Five patients had undergone repeated surgical excisions ranging from 2 to 9 in number. All but one remain free of disease 1 to 3 years after treatment with neutrons for recurrent disease. One patient with "mixed" parotid tumor has a 20% regression of her pharyngeal mass but complete disappearance of a 7 cm neck node.

In addition to repeated surgical procedures 3 patients had received prior irradiation with photons. All of these did poorly and died within a year of treatment.

Of 4 patients who received neutrons as boost therapy, only 1 is alive and well (25%). Of those who received neutrons alone, 12 of 18 patients are alive and well (66%). Two of the 5 patients in the neutrons alone group that recurred, developed disease at the periphery of the irradiated volume. Computerized scans of the irradiated volume in both patients revealed no evidence of disease in that region.

Side Effects: Only 2 patients developed necrosis, one of the tonsillar region and another in the neck. The latter occurred in a patient who had received 9000 rads of photons prior to his treatment with neutrons. Conservative management in this patient resolved his problem. The other patient developed an ulceration 3 months post radiation and has a persistent problem.

No other severe side effects were encountered, and no late complications appeared.

DISCUSSION.

The medical literature is replete with reports regarding problems of local control in this relatively rare, but aggressive, neoplasm.⁴ Local recurrence followed by widespread metastasis has been the cause of death in the majority of cases.

Locally advanced tumors have often regressed very slowly following irradiation, therefore branding the tumors as "radio-resistant". This apparent radioresistance may be due to the time period involved for cell turnover to occur rather than an inherent limitation in the response of the tumor.

Encouraging reports regarding local control of very small and localized tumors amenable to surgical removal have cited control rates from 30% to 60%. An attempt at radical removal of the larger malignant neoplasm usually compromises the nerve which is intricately entrapped by the tumor.⁴ A combination of less radical surgery and pre- or post-operative radiation has resulted in local control rates ranging from 30% to 80% dependent on the volume of gross disease left behind after surgical removal.

Based on improvements in results, various authors have outlined the indications of post-operative radiotherapy. Fu and Liebel et.al., have observed a drastic decrease in the incidence of local recurrences by the routine addition of radiotherapy to surgery as part of the initial management.⁷ Similar results have been quoted by Guillamondegui, Elkon, Rafla and Kagan in the United States.^{1, 8, 9, 10} These observations have been duplicated from across the Atlantic by Glanzmann, Catania, Jeleniewska, and others.^{11, 12, 13}

The possible role of fast neutrons in the treatment of salivary gland tumors first came to light in 1975 when Catterall reported control rates as high as 90%.¹⁴ Most of the tumors treated by her were advanced and quite similar to those being reported in this series. The cosmetic and functional results were good and no late complications occurred.

The results cited in our series appear to be superior to those reported by Parker et. al., from Seattle.¹⁵ Our series proves the efficacy of neutrons irrespective of the tumor volume in contradistinction to the data by Parker et. al, suggesting that only smaller tumors were well controlled. In our series tumors as large as 8 to 10 cm have regressed completely and have not recurred in this

period of follow-up. This is in agreement with results reported by Catterall. To-date no other technique has yielded such promising results. Fast neutrons have opened a new avenue for the patient with advanced disease and should be explored further in this respect.

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TABLE I

Site of Involvement

Parotid	Submandibular	Minor
15	2	5

TABLE II

Pathology

Histology	Number
Adenoidcystic	9
Mucoepidermoid	5
Adenocarcinoma	3
Acinic cell carcinoma	3
Mixed parotid	1
Anaplastic	1

TABLE III

Results with Neutron Boost After Photons

RESULT: 1/4 NED

No.	Site	Histology	Size of Disease	Primary/Recurrent (Date)	Photons/Neutrons	Status (Date)
76- 024	Parotid	Adenocarcinoma	Gross	Recurrent (10/76)	4400/700	DOD (2/78)
77- 105	Parotid	Mucoepidermoid	Gross	Recurrent (10/77)	4400/900	Rec. (3/79)
77- 043	Parotid	Adenocystic	Residual	Post-op. (3/77)	5000/750	NED (3/80)
78- 207	Parotid	Mucoepidermoid	Residual	Post-op. (10/78)	5000/600	DOD (2/79)

TABLE IV

Primary Disease Treated with Neutrons Only

RESULT: 5/7 NED

No.	Site	Histology	Size of Disease	Primary/Recurrent (Date of Treatment)	Neutrons	Status (Date)
77-008	Hard palate	Adenocystic	Gross	Primary (1/77)	2300	DOD (5/78) Pers. Dis. DM+
77-052	Parotid	Mucoepidermoid	Gross	Primary (4/77)	2200	NED (4/80)
79-001	Parotid	Acinic cell	Gross	Primary (1/77)	2200	NED (3/80)
79-007	Buccal mucosa	Mucoepidermoid	Gross	Primary (1/77)	2400	NED (2/80)
79-103	Parotid	Adenocystic	Gross	Primary (5/79)	2400	Recurrence (4/80) DM+
78-148	Base of Tongue	Adenocystic	Gross	Primary (10/78)	2350	NED (4/80)
79-009	Base of Tongue	Adenocystic	Gross	Primary (1/79)	2520	NED (4/80)

TABLE V

Post-operative Management with Neutrons Only

RESULT: 2/3 NED

No.	Site	Histology	Previous Management	Present Size of Disease	Neutron Dose (Date)	Results
77-053	Parotid	Anaplastic	Superficial Parotidectomy	Gross	2100 (4/77)	DOD (11/77)
78-057	Parotid	Mucoepidermoid	Superficial Parotidectomy	Microscopic Residual	2400 (5/78)	NED (4/80)
78-094	Parotid	Adenocystic	Superficial Parotidectomy	Microscopic Residual	2200 (6/78)	NED (3/80)

TABLE VI

Neutrons After Multiple Surgical Excisions

RESULT: 4/5 NED

No.	Site	Histology	Previous Management	Present Size of Disease	Neutron Dose (Date)	Results
77-002	Floor of mouth	Adenocystic	1953 - 1976 9 surgeries	2.5 cm	2200 (1/77)	NED (4/80)
77-098	Submax.	Adenocystic	1971 - 1977 3 surgeries	2 cm nodes	2100 (10/77)	NED (4/80)
78-004	Parotid	Mixed	1973 - 1977 2 surgeries	7 cm nodes 5 cm pharyn. mass	2200 (1/78)	NED -neck (4/80) Pharynx - 20% regr.
78-239	Parotid	Adenocystic	1976 - 1978 2 surgeries	3 cm	2400 (12/78)	NED (4/80)
79-035	Submax.	Adenocystic	1975 - 1979 4 surgeries	2 cm nodes	2400 (3/79)	NED (2/80)

TABLE VII

Neutrons After Surgery and Prior Radiation

RESULT: 0/3 NED

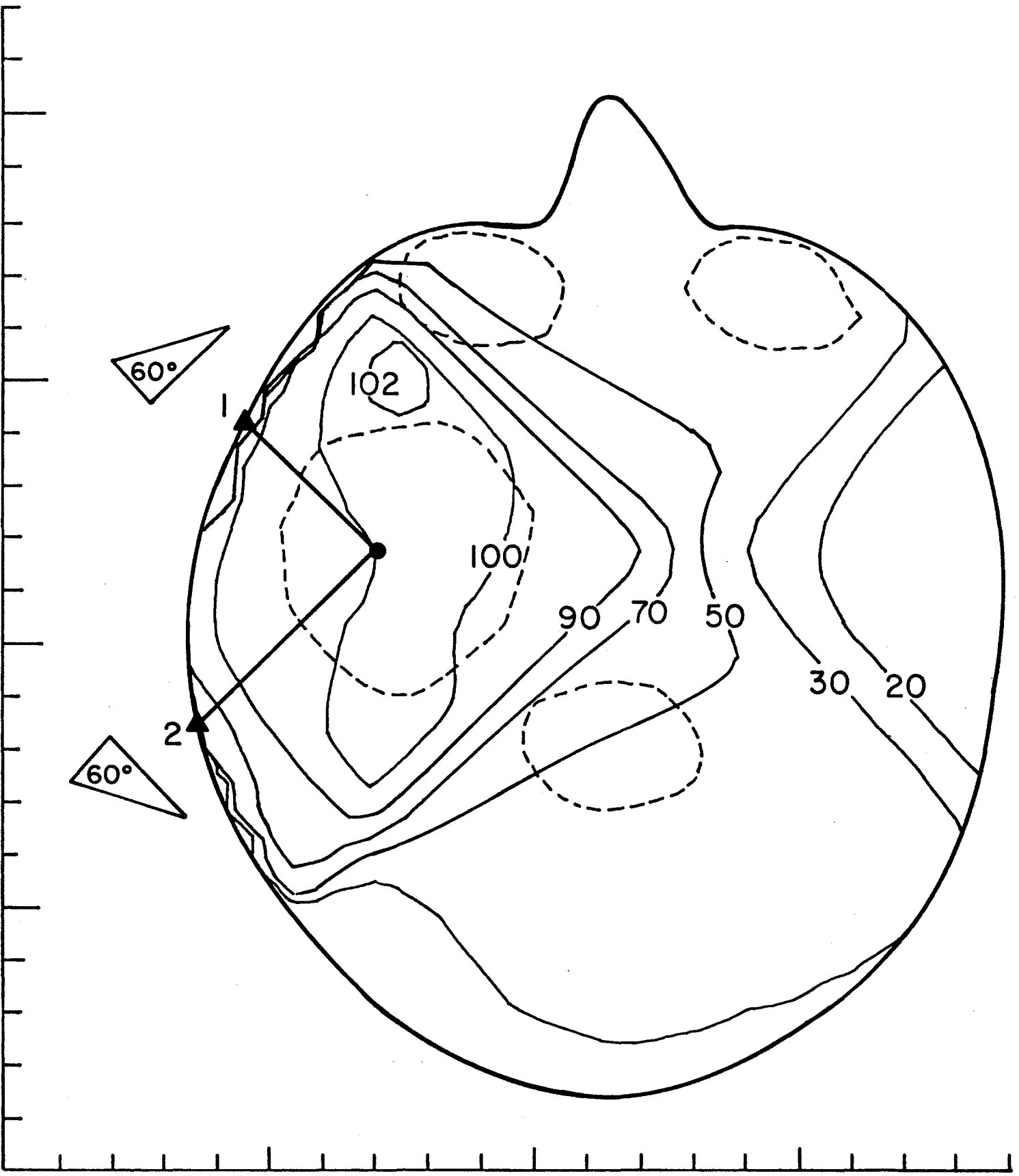
No.	Site	Histology	Previous Management	Present Size of Disease	Neutron Dose (Date)	RESULTS
77-037	Submax.	Acinic cell	1976 - Surgery 1977 - 1400 Photons	6 x 10 cm Bony destruction	2050 (4/77)	DOD (9/77) No response
77-100	Parotid	Adenocarcinoma	1975 - Surgery Post-operative radiation 5000	Base of skull involved	2200 (9/77)	NED (9/78)
78-122	Parotid	Acinic cell	1973 - 1978 4 surgeries 1975 - 5000 1976 - 4000 chemotherapy	4 - 6 cm	2000 (6/78)	DOD (6/79)

TABLE VIII

Side Effects

Symptom	Number of Patients	Degree of Severity
Loss of hair	All	Minor
Pigment alteration	1	Severe
Fibrosis (Subcutaneous tissue)	2	1 Moderate 1 Severe
Trismus	2	Minor
Loss of hearing	1	Minor
Necrosis	2	Severe

FIGURE 1



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