

RADIATION THERAPY ONCOLOGY GROUP

RTOG 80-01

A RANDOMIZED STUDY OF NEUTRONS AND CONVENTIONAL
 RADIOTHERAPY IN MALIGNANT INOPERABLE, RECURRENT,
 AND UNRESECTABLE SALIVARY GLAND TUMORS

(A cooperative study with the
 EROTC - high LET group)

Study Chairman: Thomas Griffin, M.D.
 Study Co-chairman: Professor William Duncan

Activated: July 14, 1980
 Current Edition: July 14, 1980

REPOSITORY Fermi Lab -
Neutron Therapy Facility
 COLLECTION Neutron Therapy Experiment
Protocols
 BOX No. Binder on Shelf Room GW-113
RTOG Protocol Copies
 FOLDER Copied 4/20/94 at Fermilab
NTF

0016001

INDEX

Schema

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluation
- 5.0 Randomization
- 6.0 Treatment
- 7.0 Endpoints of Study
- 8.0 Study Parameters
- 9.0 Data collection and Follow-up schedule
- 10.0 Statistical Considerations
- 11.0 Central Pathology Review
- 12.0 Additional Therapy

References

- Appendix I - Staging of Parotid Tumors
- Appendix II - Patient Consent Form

0016002

REVISIONS/CLARIFICATIONS

RTOG 80-01: NTN Parotid

September 3, 1981

Eligibility

Patients must have gross disease (i.e. measurable or macroscopically evaluable) to be eligible. Patients with only microscopic residual disease are ineligible.

0016003

RADIATION THERAPY ONCOLOGY GROUP

RTOG 80-01

A RANDOMIZED STUDY OF NEUTRONS VS CONVENTIONAL
RADIOTHERAPY IN INOPERABLE, RECURRENT
AND UNRESECTABLE MALIGNANT TUMORS OF THE SALIVARY GLANDS

Stratify

Surgical Status
Inoperable/unresectable
Recurrent
Stage
T1 - T2
T3 - T4

Histology

Squamous or malignant
mixed vs. other

R
A
N
D
O
M
I
Z
E

A. Photons
7000 rad/7 wks
or
5500 rad/4 wks
B. Neutrons
2000(Fermilab) rad/8-12
fractions/26 days

Eligible: Age: $\geq 18 \leq 75$ yrs
Histology: Malignant salivary gland tumors.
Stage: Recurrent, unresectable, inoperable.
Functional status: ≥ 60 Karnofsky score.
Prior therapy: May have had previous surgery.

To randomize patients phone RTOG Headquarters (215) 574-3191 between 9:00
am and 5:00 pm, ET.

0016004

1.0 INTRODUCTION

1.1 Rationale

Tumors of the salivary glands are relatively uncommon. The best available treatment until the present has been surgical resection of the growth whenever possible. A high local recurrence rate had been noted after surgical excision, and for this reason it was generally recommended that surgical resection be followed by high-dose radiation to the operative site. Tumors which were too large for resection were treated by external radiation, interstitial implantation or combinations of these modalities to maximally tolerated doses. Like adenocarcinomas of the GI tract, salivary gland tumors can be controlled only with high radiation doses of the order of 6500 rad in 6- 1/2 weeks and greater.

Control rates in resected tumors followed by postoperative radiation are reasonably good (90% cancer free after five years), but non-resectable tumors treated with conventional radiation alone are less effectively controlled.

Because of the relative radioresistance of these tumors and their limited response to photon radiation, neutron irradiation has been suggested as a superior treatment modality. Experience at the Hammersmith Hospital in London confirms this expectation. In Dr. Mary Catterall's series virtually all non-resectable or recurrent salivary gland tumors irradiated with the standard Hammersmith technique (1560 neutron rad in 12 fractions over 26 days) regressed completely without subsequent recurrence following neutron irradiation. In order to clarify the benefit of neutrons in this disease, a prospective randomized protocol is proposed, using conventional high dose photon irradiation (with the option of one of two fractionation techniques according to the

0016005

current convention of the participants) vs. neutron irradiation with the Hammersmith fractionation regimen (1560 rad/12f/21 days). - adjusted according to the characteristics of the various beams.

1.2 Tumor Classification

According to the World Health Organization classification, six histopathological types of salivary gland tumor are commonly encountered.* These include:

1. Mucoepidermoid carcinomas (25% of all salivary tumors), which can be low grade tumors developing slowly over many years, and presenting as a painless mass, usually in the parotid gland, or a relatively high grade rapidly growing malignancy with pain, local invasion and cervical lymph node involvement and distant metastasis.
2. Acinic cell carcinomas (15%), are low grade tumors usually limited to the parotid gland. Facial nerve involvement and metastases are rare.
3. Adenocystic carcinomas (15%), are relatively slow growing, though aggressive, tumors with a high propensity for invasion of lymphatics and perineural spaces. They are the most common malignant tumors in submaxillary and minor salivary glands.
4. Malignant mixed salivary tumors (12%) are slowly growing and locally infiltrating, with frequent regional and distant metastasis. They exhibit a very high local recurrence rate following resection.
5. Adenocarcinomas (10%) are highly malignant, rapidly invading and metastasizing tumors, usually associated with nerve involvement.
6. Squamous carcinomas (23%) are rapidly growing, painful, infiltrating tumors which produce nerve palsy and extensive cervical node metastasis relatively early.

*"Histologic Typing of Salivary Gland Tumors," A.C. Thockray in collaboration with L.H. Sobin, 1972; World Health Organization.

Each of the above histopathological types can occur in any of the following anatomical sites: parotid gland, submaxillary gland, minor salivary glands in the oral cavity, oropharynx, hypopharynx, larynx and paranasal sinuses. Similar tumors have been observed in the lacrimal glands and rarely in other head and neck sites.

2.0 OBJECTIVES

- 2.1 To measure the control rate and disease free interval of measurable salivary gland tumors to neutrons as compared to photons.
- 2.2 To measure the morbidity of irradiation with neutrons compared to photons.
- 2.3 To measure the survival of patients treated with neutrons compared to photons.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Inoperable, unresectable or recurrent salivary gland malignancy. Tumor may involve major or minor salivary glands. Primary irradiation is indicated in patients with gross tumor when the disease is inoperable due to extent of the primary tumor, or there are medical contraindications to surgical treatment, or because of recurrent growth following primary surgical treatment.
- 3.1.2 Age \geq 18 and \leq 75 yrs
- 3.1.3 No previous malignancy (except skin cancer) unless disease free for 5 years or longer.
- 3.1.4 No previous irradiation to the site of interest
- 3.1.5 Karnofsky status \geq 60%

0016007

3.2 Ineligibility Criteria

The following ineligibility criteria exclude the patient from the protocol:

- 3.2.1 Metastatic disease (other than cervical lymph nodes)
- 3.2.2 Histology other than listed under "Classification" (Section 1.2); e.g., pleomorphic adenoma, oncocytoma.
- 3.2.3 Medical contraindication to a full course of irradiation (Section 6.0).

4.0 WORKUP AND PRETREATMENT EVALUATION

- 4.1 History and physical exam (head and neck exam to include palpation of oropharynx).
- 4.2 Staging of primary and regional nodes (see Appendix I).
- 4.3 Drawing of primary tumor or residue and regional lymph nodes with centimeter measurements.
- 4.4 Photograph of lesion if possible.
- 4.5 Radiographic evaluation
 - 4.5.1 Chest x-ray
 - 4.5.2 Mandible x-ray
 - 4.5.3 Base of skull (for adenocystic)
 - 4.5.4 CT scan thru tumor volume (if available).
 - 4.5.5 Other radiographic studies as determined by site of origin of tumor (e.g. sinus film for palatal tumors, or soft tissue lateral for tumor of parapharyngeal space).

5.0 STRATIFICATION AND RANDOMIZATION

- 5.1 Stratification will be by surgical status (inoperable, unresectable vs. recurrent), stage (T1 - T2 vs. T3 - T4), histology (squamous or malignant mixed vs. other).

0016008

5.2 Randomization

To randomize a patient call RTOG Headquarters (215/574-3191) between 9:00 a.m. and 5:00 p.m. ET and give the following:

Investigator's name

Patient's name

Neutron facility

Institution referring patient

Surgical status (inoperable, unresectable, recurrent)

Stage (T1, T2, T3 or T4)

A project case number and treatment assignment to either photons or neutrons will be given by telephone and confirmed by mail.

If photons are assigned, treatment may be delivered at the referring institution.

6.0 RADIATION THERAPY

6.1 Photon Energy - supervoltage (> 1 mev) photons are to be used with a minimum SAD of 80 cm. Electrons can be used with or without photons so long as the dose and target volume criteria are met.

6.2 Dose

6.2.1 Dose Specification

Doses will be target absorbed dose that is the central dose as specified in section 3.3 of ICRU report 29. A +5% variation of dose across the primary target volume is permissible.

6.2.2 Photons

One of two fractionation schedules may be selected according to the current policy of the institution. However, the schedule must be selected prior to participation in the protocol and must be used for all cases accessed to the study that are randomized to receive photons.

When there is measurable disease, the target absorbed dose is 7000 rad/7-8 weeks -NSD 1880-1950

0016009

rets (or 5500 rad in 4 wks.-NSD 1880 rets). A reduced field may be used at 6000 rad (or 5000 rad with the shorter schedule), encompassing gross residual disease. All fields must be treated at each session.

6.2.3 Neutrons - The dose will be delivered in 12 fractions using three fractions per week (over 26 days). If the neutron beam is not available three times per week then the dose will be delivered in 8 fractions using two fractions per week (over 26 days). The following target absorbed doses (total dose) will be delivered:

Facility	Total Dose (n + γ)
Fermilab	2050
Tamvec	1950
Glanta	1875
Amsterdam, Hamburg, Manchester	1750
Seattle	1700
Edinburgh, Essen	1650

6.3 Volume

For the parotid gland, the area to be irradiated shall include the entire parotid bed and full extent of the surgical scar if any. To spare the opposite parotid, the volume should be treated using a wedged pair or similar arrangement of treatment fields, unless not technically feasible. All gross tumors will be included with a 2 cm margin. The fields will extend from the ridge of the zygoma superiorly, down to the angle and horizontal ramus of the mandible inferiorly. The anterior margin of the field shall extend at least as far as the anterior border of the masseter muscle, approximately 6 cm anterior to the external auditory meatus. The posterior margin shall extend to the mastoid process. Typically, the target volume measures 8 x 10 cm on the surface and extends to a depth of 5 or 6 cm. Individual treatment plans may vary, but typically this volume is best encompassed using a pair of

0016010

wedged, angled fields converging at the base of the tumor.

In the case of non-parotid/salivary gland tumors the primary with a 2 cm margin, or the bed of the tumor if done after excision, must be included. If a scar recurrence is a concern then the scar should be included in the primary target volume.

6.4 Cervical nodes

Regional nodes must be irradiated whenever they are obviously affected. Except for early, low-grade mucoepidermoid or "benign" mixed salivary tumors, the regional nodes may be irradiated when there is a high probability of occult microscopic disease. Inclusion of non-palpable draining lymph nodes is necessary for submandibular but not palatal tumors.

6.4.1 Volume

In most cases the nodes can be treated with a downward extension of the portal designed to include the primary growth. If the lesion is anaplastic or there is known caudal extension of the tumor, a contiguous anterior supraclavicular field on the affected side and treated with photons is recommended. This field should be large enough to extend the irradiated volume to include the remainder of the cervical lymph node chain not included in the primary target volume, but will exclude midline structures. This is best effected by means of a single anterior field treated with photons with its upper margin matched to the primary target volume.

6.4.2 Dose

The dose to palpable cervical nodes (i.e. N+) should be the same as to the primary target volume. Nonpalpable nodes should receive 5000 rad (calculated at Dmax) in 5 to 5-1/2 weeks using photons or the equivalent neutron dose (or 4000 rad with the shorter schedule).

0016011

7.0 ENDPOINTS OF STUDY AND RESPONSE CRITERIA

7.1 Gross disease will be measured by degree of control (i.e. complete response) and disease free interval.

7.1.1 Complete response (CR) - complete disappearance of all measurable and palpable tumor.

7.1.2 Partial response (PR) - reduction in size to at least 50% of the product of the two largest perpendicular dimensions.

7.1.3 No response (NR) - < 50% reduction to < 25% increase of the product of the two largest perpendicular dimensions.

7.1.4 Progression - increase in size > 25% of the product by the two largest perpendicular dimensions.

Due to the different fractionation schedules, response will be measured from the start of radiotherapy.

7.2 Late effects within the irradiated volume will be scored at each follow-up using the RTOG scale.

8.0 STUDY PARAMETERS

<u>Parameter</u>	<u>Pre-Rx</u>	<u>At Completion</u>	<u>At follow-up</u>
Measurement of tumor	x	x	x ^a
Intraoral photography	x ^a		x ^a
Photographs of treated skin	x	x	x
Chest X-ray	x		x ^b
Chemistries	x ^a		x ^b
Mandible X-ray	x ^a		x ^b
Base of skull X-ray	x ^a		x ^b
CT scan	x ^c		x

(a) If appropriate

(b) If abnormal at start

(c) If available

0016012

9.0 DATA COLLECTION AND FOLLOW-UP SCHEDULE

A copy of each study form must be submitted to RTOG Headquarters according to the schedule in 9.6. Data will be recorded on standard RTOG forms to be supplied to each participating institution. The following records will be generated by the study team and participating institutions:

9.1. On-study form.

9.2 Treatment prescription.

9.3 Localization Film. Localization films of each field will be taken and sent to the RTOG office in the first week of therapy together with a copy of the treatment plan.

9.4 Treatment Summary Form.

9.4.1 Radiation therapy flow sheet including type of energy, daily schedule of treatment, maximum dose, any complications during radiation therapy and their management, a description of the lesion at the end of treatment, copies of port films and isodose distributions etc.

9.4.2 Operative procedures and findings, if applicable (extent of disease, presence of metastases, type and extent of surgery performed, etc.).

9.4.3 Drugs administered, if any (a description of type and dose of any drugs administered, duration, and purpose, including any chemotherapy administered in the event of lack of tumor control).

9.5 Follow-up Assessment Form

9.5.1 Follow-up schedule

Patients will be seen 1 month after completion of treatment, and 2 months thereafter for the 1st year; every 3 months for the 2nd and 3rd year, every 4 months for the 4th and 5th year and yearly thereafter.

9.6 Death Form

This will include date and cause of death with particular reference to intercurrent illness, primary cancer or metastases.

0016013

Summary of Forms Submission.

<u>Form</u>	<u>Due</u>
On-study form	Within one week of randomization
Radiotherapy prescription	
Copies of localization films	
Pathology slides and report	
Operative report	
Treatment summary form	Within two weeks of completion of
Copy of radiotherapy record	radiotherapy
Copy of boost fields	
Isodose distribution	
Follow-up assessment	Within two weeks of times in 9.5.1.
Death form	Within one month of death

10.0 STATISTICAL CONSIDERATIONS

It is the impression of clinicians that the historical rate of local control for unresectable salivary gland tumors has been approximately 20% with the best photon radiotherapy. Pilot studies of neutron treatment indicate a local control rate as high as 60% or even higher.

In order to detect an improvement of this magnitude with a high degree of certainty (i.e. at least 90%) using a one-sided significance level of $p=0.05$, a sample size of 22 patients per arm is required. It is estimated that this number of patients would accrue in less than two years.

The patients entering this protocol might not be strictly comparable to those who entered the pilot studies. For this reason, it is possible that the degree of improvement in the control rate could be less dramatic than in the pilot studies. In order to detect a more modest (but still clinically important) improvement to 50% local control would require 39 patients per arm.

Under the assumptions of 90% power and a one-sided level of significance $p=.05$, the sample sizes needed to detect a significant difference between groups having local control rates P_1 and P_2 are given below:

<u>P_1 = rate for standard treatment</u>	<u>P_2 = rate for experimental treatment</u>	<u>N = sample size (per arm)</u>
.2	.4	86
.2	.5	39
.2	.6	22
.2	.7	13
.2	.8	8

11.0 CENTRAL PATHOLOGY REVIEW

Central pathology review will be required of all patients randomized. A representative slide and pathology report must be submitted within one week of randomization. A pathologist will be selected by each the RTOG and the EORTC high LET committee to minimize the transatlantic transport of slides. A random number of cases will be reviewed by both pathologists to assure uniformity of reporting.

12.0 ADDITIONAL THERAPY

Therapy is to be administered as detailed in section 6.0. Subsequent therapy shall proceed at the discretion of the patient's responsible physician. Indications for subsequent therapy and the therapy performed should be documented in the patient's follow-up records. Clinical evidence of lack of tumor control should be documented in the patient's follow-up records.

APPENDIX I

STAGING OF SALIVARY GLAND

American Joint Committee for Cancer Staging
and End-Results Reporting (1978)

STAGING

Primary Tumor (T)

- T0 No evidence of primary tumor;
- T1 Tumor 2 cm or less in diameter, solitary, freely mobile, facial nerve intact^{*}
- T2 Tumor more than 2 but not more than 4 cm in diameter, solitary, freely mobile or reduced mobility or skin fixation, and facial nerve intact ;
- T3 Tumor more than 4 but not more than 6 cm in diameter, or multiple nodes, skin ulceration, deep fixation, or facial nerve dysfunction^{*} ;
- T4 Tumor more than 6 cm in diameter and/or involving mandible and adjacent bones;

(* applicable to paratoid tumors only)

Nodal Involvement (N)

In clinical evaluation, the actual size of the nodal mass should be measured and allowance should be made for intervening soft tissues. It is recognized that most masses more than 3 cm in diameter are not single nodes but are confluent nodes or tumor in soft tissues of the neck. There are three stages of clinically positive nodes: N1, N2 and N3. The use of subgroups a, b and c is not required, but is recommended. Midline nodes are considered as homolateral nodes.

- NO No clinically positive nodes;
- N1 Single clinically positive homolateral node 3 cm or less in diameter;

- N2 Single clinically positive homolateral node more than 3 but not more than 6 cm in diameter or multiple clinically positive homolateral nodes none more than 6 cm in diameter;
 - N2a Single clinically positive homolateral node, more than 3 but not more than 6 cm in diameter;
 - N2b Multiple clinically positive homolateral nodes, none more than 6 cm in diameter;
- N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s);
 - N3a Clinically positive homolateral node(s), one more than 6 cm in diameter;
 - N3b Bilateral clinically positive nodes (in this situation, each side of the neck should be staged separately; that is, N3b: right, N2a; left, N1).
 - N3c Contralateral clinically positive node(s) only.

Distant Metastases (M)

- M0 No (known) distant metastasis;
- M1 Distant metastasis present.

Specify _____

APPENDIX II

SAMPLE CONSENT FORM FOR SALIVARY GLAND TUMORS

You have been found to have a malignant tumor of one of your salivary glands. These tumors are responsive to radiation treatments. They can be treated with either the routine type of radiation or with a new type of radiation called neutrons. There are only a few neutron machines in the U.S. There have been very encouraging reports from England to indicate that neutrons may be more effective than routine radiation. However, this has not been confirmed in the U.S. In order to solve this problem, your doctors would like you to participate in a study in which the decision of which type of radiation you receive is made at random (by chance).

The side effects of both types of treatments are about the same and depend on the location of the tumor. For tumors of the parotid glands side effects may include stiffness of the jaw, dryness of the mouth, redness of the skin over the area being treated, hearing difficulty and dryness of the ear canal. There are no good alternatives to this treatment.

The advantage of participating in this study is that you might receive a superior treatment method - the disadvantage is that the neutron therapy may be inconvenient and may not work.

Think over what you have read this hospital and institution where I am being treated does not provide compensation for any treatment disability incurred as a result of participating in this research.

M/disk 16 #13

0016018