

RADIATION THERAPY ONCOLOGY GROUP
RTOG #82-02

PHASE I/II DOSE SEARCHING STUDY OF FAST NEUTRON IRRADIATION
IN THE TREATMENT OF ADVANCED HEAD AND NECK CANCER

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IN THE TREATMENT OF ADVANCED HEAD AND NECK CANCER

SCHEMA

R		T	
E		R	Step 1*
C	Region	E	15.75 Gy (neutrons) in 12 fractions in 26 days
O		A	Step 2**
R	Stage	T	17.50 Gy in 12 fractions in 26 days
D		M	Step 3**
		E	19.25 Gy in 12 fractions in 26 days
		N	
		T	

*see 6.1.5 for facility adjustments

**may be adjusted on basis of results from Step 1.

Eligible:

Region: Oral Cavity
Oropharynx
Hypopharynx
Larynx

Stage: III, IV and Stage II Base of Tongue

Histology: Squamous cell carcinoma

Age: > 18

Performance: Karnofsky \geq 50

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1.0 INTRODUCTION

Patients with advanced head and neck cancer have a poor prognosis with many dying of uncontrolled local cancer. High dose conventional photon therapy, while being effective in early head and neck tumors fails in the majority of advanced cancers. These large and frequently ulcerated and necrotic tumors are believed to contain radioresistant viable hypoxic cells. These cells have an oxygen enhancement ratio (OER*) of 2.5 to 3. Neutron therapy should be more effective in treating hypoxic tumors because its lethal effect on cells is much less dependent on the presence of oxygen (it has an OER of 1.6).

Catterall et al.^{1,2} achieved a significantly better local control with neutron therapy as compared to photons in a randomized trial of squamous carcinoma of the head and neck. Seventy-six percent of the patients treated with neutrons remained locally controlled versus only 19% of the patients treated with photons. The neutron dose was 1560 cGy given in 12 fractions over 4 weeks. (Since Hammersmith investigators report only the neutron component of the beam and US investigators report total radiation delivered i.e., $n + \gamma$, this is equivalent to 1700 cGy total dose - $n + \gamma$ when the same energy of beam is used.)

Pilot studies in the U.S. with neutrons alone had a significant rate of complications.^{3,4} At M.D. Anderson Hospital, 66 patients were treated with neutrons alone. Of these, 49 had two fractions a week and were treated between 1972 and 1975. A later group of 17 patients were treated in 1976 with four fractions a week. The weekly dose in all patients was 320 cGy with a mean of 2089 cGy over 6 1/2 weeks. There were 18% (9/49) complications in the earlier group of 49 patients, and one complication in the 17 patients treated with four fractions a week. Local control was achieved in 42% of the 66 patients.

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The poor physical characteristics of the neutron beam (horizontal beam, increased absorption in fat, and greater penumbra) as well as the altered fractionation scheme were believed to contribute to the increased number of complications. To improve on these deficiencies, a mixed-beam arm was included in protocol 76-10. The other two arms were neutrons alone and conventional therapy with photons. In the mixed-beam arm, patients were treated daily with a loading of 3:2 photons to neutrons. In a recent report (Seattle, August 4-5, 1981) to the RTOG High-Let Committee, there were available data on 145 patients treated with mixed-beam and 199 patients treated with photons. Only 22 patients were treated with neutrons alone. There was no difference in local control and survival comparing mixed-beam and photons.

A return to neutrons alone studies seems appropriate at the present for the following reasons: (1) better neutron beams will be available soon in a number of institutions overcoming some of the physical deficiencies in previously used cyclotrons, (2) a better understanding of the radiobiology of fast neutron irradiation. Specifically, the knowledge gained that the RBE of neutron therapy depends on the tissue irradiated and the type of reaction or endpoint chosen, and (3) the necessity to repeat the widely quoted, very favorable Hammersmith experience headed by Dr. Catterall.

It is for this last reason that a fractionation schedule as used at Hammersmith will be chosen for this Phase II study. The shortened overall treatment time will have the theoretical advantage of overcoming some of the repopulation of the cancer cells occurring during more prolonged treatment. The lower number of fractions should not compromise the effectiveness of the treatment because neutrons are less dependent on reoxygenation and redistribution within the tumor. Late damage to normal tissues is expected to be the same regardless of the number of fractions.⁵ This is explained by the non-repairable cell kill mode of neutron irradiation.

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The present Phase II study is designed to find the most appropriate dose to be used for later randomized Phase III studies. The first step of the present trial will be to utilize a 90% dose level of the one used at Hammersmith. Thirty to 40 patients will be accrued for the first step and scored for acute reactions, overall clinical tolerance and tumor clearance. After the last patient has been treated, a second group of patients will be treated with a 5-10% higher dose. Further groups of patients may be treated with higher doses based on the experience gained in the previous steps until the maximum tolerated dose is achieved. Since with this fractionation schedule, it appears that late effects will not be more than acute effects, the acute reaction will be used as an index of tolerance.

This dose-searching process is mandatory as firsthand knowledge of reactions to shortened fractionation schemes is lacking in this country. The 10% dose reduction in the first step of the study, as compared to the Hammersmith dose, is designed to offset possible increased reactions due to differences in technique and volumes treated.

Once the appropriate total dose is determined from this study, a Phase III comparison of this four week neutron treatment will be studied against the best photon scheme.

2.0 OBJECTIVES

- 2.1 To determine the optimum total neutron dose using 12 fractions over four weeks.
- 2.2 To assess local tumor control.
- 2.3 To assess acute reactions.

3.0 PATIENT SELECTION

3.1 Eligibility.

- 3.1.1 Sites (see Appendix I).
 - 3.1.1.1 Oral Cavity - Stage III, IV.
 - 3.1.1.2 Oropharynx - Stage III, IV (Base of Tongue - Stage II also).

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- 3.1.1.3 Hypopharynx - Stage III, IV.
 - 3.1.1.4 Larynx (including supraglottis) - Stage III, IV.
 - 3.1.2 Biopsy proven carcinoma.
 - 3.1.3 No previous radiation therapy.
 - 3.1.4 No previous chemotherapy.
 - 3.1.5 No evidence of metastatic disease.
 - 3.1.6 No plan for resection of primary following irradiation.
 - 3.1.7 Age > 18 but there will be no upper age limit as long as general medical requirements (3.2.6) are met.
 - 3.1.8 Performance Status (Karnofsky) \geq 50.
- 3.2 Ineligibility Criteria.
- Patients are eliminated from the study for the following reasons:
- 3.2.1 Tumor is classified Stage I or II, except base of tongue primary where Stage II is eligible.
 - 3.2.2 Patients with distant metastases.
 - 3.2.3 Patients with two simultaneous tumors, regardless of location of second primary.
 - 3.2.4 Previous radiation therapy of the head and neck, except for skin cancer, or patients receiving prior chemotherapy.
 - 3.2.5 Prior surgery (except diagnostic) to primary site or nodes.
 - 3.2.6 General medical reasons:
 - 3.2.6.1 Poor general condition indicated by a Karnofsky performance status less than 50 (eg., severe malnutrition, below 60% standard weight) or conditions which in the investigator's opinion precludes any curative effort.

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4.0 PRETREATMENT EVALUATION

- 4.1 Complete history and physical exam with an assessment of the patient's performance status. Diagrams of the primary and any nodal metastases must be made.
- 4.2 Imaging Studies
 - 4.2.1 Required
 - 4.2.1.1 Chest x-ray
 - 4.2.1.2 Liver scan if liver enzymes are elevated
 - 4.2.1.3 Other pertinent radiographs depending on location of primary
- 4.3 Satisfactory biopsy of the primary
- 4.4 Dental care

5.0 REGISTRATION

- 5.1 Patients should be registered prior to treatment by calling RTOG Headquarters (215/574-3191) between 9:00 A.M. and 5:00 P.M. ET. The following information will be required:
 - Principal Investigator's Name
 - Institution
 - Protocol
 - Patient's Name
 - Site and Region of Tumor
 - Stage

A project case number will be assigned which will be confirmed by mail.
- 5.2 Treatment should begin within 14 days after registration.

6.0 TREATMENT

- 6.1 Radiotherapy.
 - 6.1.1 Localization requirements.
 - 6.1.1.1 Simulation of treatment fields is desirable but not mandatory. The field borders must initially include the entire primary region (e.g. tongue/oropharynx) and bilateral cervical nodes. For all pyriform sinus (hypopharyngeal) primaries

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and for all T4 tonsillar lesions, the superior field must extend to the base of the skull. The superior, posterior field border must at least encompass the mastoid tip. The entire neck must be treated to the superior edge of the clavicles. Separate anterior supraclavicular fields should be used.

6.1.1.2 Verification ("beam") films must be obtained on each treatment portal irradiated including all cone-down or boost fields (except those using electron therapy). These should be repeated weekly and at the time of any adjustments.

6.1.2 Target volume. Irradiation Portals.

Radiotherapy portals must initially encompass the entire primary tumor region plus the bilateral cervical lymph node chains with the upper posterior border set at least at the posterior aspect of the mastoid process. Treatment portals will include the prevertebral soft tissues to the base of skull for all pyriform sinus (hypopharynx) and T-4 tonsillar primaries. The supraclavicular regions must be treated via an anterior portal with spinal cord shielding. (Lymph node areas not containing palpable nodes and not within the field used to treat the primary tumor should be treated with photons or electrons.)

6.1.3 Dose calculations

6.1.3.1 Doses are specified as mid-depth at central axis when parallel opposed techniques are used or at the intersection of the central axes for other techniques (i.e. target absorbed dose as specified in section 3.3 of ICRU report 29). Complete isodose curves are required on the central

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axis and contours 2 cm from the upper and lower border must also be supplied.

6.1.3.2 Variation within the target volume should not exceed ± 10% of the target dose.

6.1.3.3 Fields must encompass the primary tumor and its suspected projections with a minimum 1.5 cm margin in all directions. This tumor (target) volume should receive 90% or greater of the central axis mid-depth dose. If areas of suspected disease are included in the target volume and a "shrinking field technique" is planned, the fields may be reduced in dimensions after 9 fractions (75% of the total dose). Fields must be reduced to exclude the spinal cord at a neutron dose of 900 cGy at midline.

6.1.3.4 The entire neck must be irradiated. Photons should be used. A dose of at least 4500 cGy (even in N₀ stages) in 20 fractions calculated at Dmax must be given. If, because of logistic reasons neutrons are used, 75% of the target absorbed dose should be given to areas not containing palpable nodes.

6.1.3.5 Time and Dose Modifications.
Treatment breaks if necessary should be allowed only for healing of severe normal tissue reactions (confluent mucositis).

6.1.4 Fractionation

6.1.4.1 Fractionation will be 3 fractions per week, giving equal daily doses. A total of 12 fractions will be given in 4 weeks. (If beam availability prevents this fractionation, 9 fractions in 4 weeks should be used.)

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6.1.5 Doses

The following target absorbed doses will be delivered in 12 fractions using three fractions per week (over 26 days). (These are adjusted on the basis of the RBE's of the beams compared to Hammersmith as well as the difference the reporting dose i.e. n vs. $n + \gamma$.)

Total Dose ($n + \gamma$)

<u>Facility</u>	<u># Fractions</u>	<u>Step 1</u>	<u>Step 2</u>	<u>Step 3</u>
Fermilab	9	----	2050	2255
*Glanta	12	1575	1750	1925
*M.D. Anderson	12	1575	1750	1925
University of Pa.	12	1575	1750	1925
Seattle	12	1530	1700	1870

*using protons on beryllium

Dose per fraction

<u>Facility</u>	<u>Step 1</u>	<u>Step 2</u>	<u>Step 3</u>
Fermilab	---	228	250
*Glanta	131	146	160
*M.D. Anderson	131	146	160
University of Pa.	131	146	160
Seattle	128	142	156

Step 1 is calculated as 90% of the dose equivalent used at Hammersmith. Step 2 is equivalent to the Hammersmith dose while Step 3 is 10% greater. The doses used after Step 1 may be modified on the basis of acute reactions and tumor response observed in the patients treated in Step 1.

7.0 DRUG THERAPY

Does not apply to this study.

8.0 SURGERY

8.1 Surgical removal of the primary or regional nodes should not be planned unless persistent cancer is proven by biopsy 6 weeks or more following completion of radiotherapy. Under

these circumstances, the patient will be considered as a treatment failure. Patients who are originally operable (suitable for a combined-treatment approach) are ineligible for this study.

9.0 OTHER THERAPY

Any other clinically indicated therapy, if performed, must be reported on appropriate RTOG forms.

10.0 PATHOLOGY

Histopathologic grading of squamous variants will be accepted according to the practice of each institution using the following synonyms:

Grade I - well differentiated or Keratinizing

Grade II - moderately differentiated or Typical

Grade III - poorly differentiated or anaplastic

"Lymphoepithelioma" will be considered a variant within the Grade III category.

Central pathology review is not planned.

11.0 PATIENT ASSESSMENTS

11.1 Endpoints of the study will include:

11.1.1 Completeness of tumor regression

11.1.2 Acute toxicity of radiotherapy

11.1.3 Local control

11.2 Measurements of Specific Endpoints

Response shall be measured as follows:

11.2.1 Local response - rate of regression of primary tumor under therapy will be determined by measurements of the primary tumor in maximum dimensions and dimensions at right angles to it, if possible; otherwise by subjective assessment of percentage regression. Response will be designated as:

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- 11.2.1.1 Complete response (CR) -
Complete disappearance of
measurable and palpable tumor.
- 11.2.1.2 Partial response (PR) - Tumor
shrinkage greater than 50% of
the product of the perpendicular
diameters of the two largest
dimensions.
- 11.2.1.3 Minor response (MR) - Tumor
shrinkage greater than 25% but
less than 50% of the product of
the perpendicular diameters of
the two largest dimensions.
- 11.2.1.4 No change (NC) - 25% growth to
25% shrinkage of the product of
the perpendicular diameters of
the two largest dimensions.
- 11.2.1.5 Progressive disease (PD) -
Growth of tumor greater than 25%
of the product of the
perpendicular diameters of the
two largest dimensions.
- 11.2.2 Status of Neck - Weekly measurements
should be made during treatment if any
measurable neck nodes are present. An
assessment should be made including:
No evidence of node enlargement in the
neck.
Residual induration in the neck.
- 11.2.3 Presence or absence of metastases by
clinical evaluation or appropriate
studies.
- 11.2.4 Toxicity of radiotherapy
Weekly assessments of mucositis and skin
reactions will be made during radiotherapy

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and following treatment until all such reactions subside. The RTOG acute scoring scale will be used (Appendix V).

11.2.5 Late effects of radiotherapy will be scored at each follow-up assessment using the RTOG-EORTC late effects scale.

11.3 Study Parameters.

<u>Parameters</u>	<u>Pre-Study</u>	<u>Weekly during Radiotherapy</u>	<u>Follow-up After Therapy Completed</u>
History & Physical Exam.	x	x	x++
Weight and Perform. Status	x	x	x++
Tumor Measurement	x	x	x++
Toxicity Notation		x	
Late Effects	x		x++
Chest X-ray	x		x+
Appropriate X-Rays for	x		x++

+Chest x-rays will be performed q 12 weeks the first year of follow-up and q 6 months thereafter.

++Clinical examination and x-rays for tumor measurements will be performed 4 weeks after treatment then q 3 months the 1st and 2nd year, q 6 months the 3rd through 5th year and yearly thereafter.

11.4 Follow-up assessments are to be reported every three months during the first two years following treatment, then every 6 months for the next three years, and annually after the fifth year. The following will be evaluated:

- a. Primary tumor site.
- b. Regional nodes.
- c. Metastatic visceral spread.
- d. Treatment complications.

Confirmation by radiographs or biopsy is preferable and agreement by two physicians of different specialties is advisable.

11.5 Additional treatment should be listed and details of management are at the discretion of physicians managing the case.

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12.0 DATA COLLECTION

Data are due according to the following schedule:

<u>Data</u>	<u>Schedule</u>
On-Study Form Preliminary Dosimetry Information: Prescription, central axes calculation, film Diagnostic Pathology Report Diagram of Primary & Regional Nodes	Within 1 week of commencement of radiotherapy
Radiotherapy Form Final Dosimetry Information: Treatment sheets, film of boost or field alterations, isodose summation (if done).	At completion of radiotherapy
Follow-up Assessment Form*	Every 3 months for 2 years, then every 6 months for 3 years, annually thereafter.

*In the event of subsequent surgery, the operative note and the operative pathology report must be submitted.

13.0 STATISTICAL CONSIDERATIONS

The purpose of this study is to determine the maximum dose which has an acceptable rate of acute severe complications and to estimate the local tumor control of this dose. Ten patients at each facility will be treated on the first dose and if no complications are observed ten additional patients at each facility will be treated on the second dose. If a severe complication is observed on any dose 15 additional patients at each facility will be treated on the next lowest dose. Using this scheme there will be 25 patients treated at each facility at the dose that will be used for the future phase III trial and with this number, there will be a 93% chance of seeing any complication that occurs with a frequency of 10%. With 25 patients the 90% confidence interval about the local control rate will be narrower than $\pm 16\%$. The initial trial of 10 patients at each lower dose will insure a 89% chance of observing any complication that occurs with a frequency of 20%.

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It is estimated that one patient per week will be accrued at each facility which will require approximately 3 months to complete each dose level.

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REFERENCES

1. Catterall, M, Sutherland, I, Bewley DK: First results of a randomized clinical trial of fast neutrons compared with X or gamma rays in treatment of advanced tumors of the head and neck. Br J Med 2:653-656, 1975.
2. Catterall, M, Bewley, DK, Sutherland, I: Second report on results of a randomized clinical trial of fast neutrons compared with X or gamma rays in treatment of advanced tumors of head and neck. Br J Med, p. 1642, 1977.
3. Laramore, GE, Blasko, JC, Griffin, TW, Groudine, MT: Fast neutron teletherapy for advanced carcinomas of the oropharynx. Int J Radiat Oncol Biol Phys 5:1821-1827, 1979.
4. Maor, MH, Hussey, DH, Fletcher, GH, Jesse, RH: Fast neutron therapy for locally advanced head and neck tumors. Int J Radiat Oncol Biol Phys 7:155-163, 1981.
5. Withers, HR, FLOW, BL, Huchton, JI, Hussey, DH, Jardone, JH, Mason, KA, Raulston, GL, Smather, JB: Effect of dose fractionation and early and late skin responses to γ -rays and neutrons. Int J Radiat Oncol Biol Phys 227-233, 1977.

APPENDIX I

Eligible Patients & 1977 American Joint Commission Staging

Eligible Patients

Oral Cavity

Stage III, IV	Tongue (Anterior) Floor of Mouth Buccal Mucosa Palate (Hard or Soft) Gingiva
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Oropharynx and Hypopharynx

Stage III, IV	Tonsil and/or pillars Suprahyoid epiglottis Pharyngeal Walls (posterior or lateral)
Stage II, III, IV	Base of Tongue Pyriiform Sinus (or medial/lateral walls) Postcricoid area

Supraglottic

Stage III, IV	Ventricular band Arytenoid Suprahyoid epiglottis Infrahyoid epiglottis Aryepiglottic fold
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Miscellaneous Category

III, IV	Maxillary Antrum
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Note: *All T-stages may be included if associated with fixed, inoperable (>6 cm) unilateral or bilateral lymphadenopathy (N_{2B} or N_{3B}).

AJC Staging

Oral Cavity

Buccal mucosa
Lower alveolar ridge
Upper alveolar ridge
Retromolar gingiva (Retromolar trigone)
Floor of mouth
Hard palate
Anterior two-thirds of the tongue

Primary tumor (T)

TX No available information on primary tumor
No evidence of primary tumor
TIS Carcinoma in situ
T1 Greatest diameter of primary tumor less than 2 cm
T2 Greatest diameter of primary tumor 2 to 4 cm

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- T3 Greatest diameter of primary tumor more than 4 cm
- T4 Massive tumor greater than 4 cm in diameter with deep invasion to involve antrum, pterygoid muscles, root of tongue, or skin of neck

- Oropharynx - Faucial arch including soft palate, uvula and anterior tonsillar pillar
- Tonsillar fossa and tonsil
 - Base of tongue including glossoepiglottic and pharyngoepiglottic folds
 - Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

Primary Tumor (T)

- TX Tumor that cannot be assessed
- T0 No evidence of primary tumor

- TIS Carcinoma in situ
- T1 Tumor 2 cm or less in greatest diameter
- T2 Tumor greater than 2 cm, but not greater than 4 cm in greatest diameter
- T3 Tumor greater than 4 cm in greatest diameter
- T4 Massive tumor greater than 4 cm in diameter with invasion of bone, soft tissue of neck, or root (deep musculature) of tongue

- Hypopharynx - Pyriform sinus
- Postcricoid area
 - Posterior hypopharyngeal wall

- TIS Carcinoma in situ
- T1 Tumor confined to the site of origin
- T2 Extension of tumor to adjacent region or site without fixation of hemilarynx
- T3 Extension of tumor to adjacent region or site with fixation of hemilarynx
- T4 Massive tumor invading bone or soft tissue of neck

- Supraglottic - Ventricular bands (false cords)
- Arytenoids
 - Epiglottis (both lingual and laryngeal aspects)
 - Suprahoid epiglottis
 - Infrahyoid epiglottis
 - Aryepiglottic folds

- TIS Carcinoma in situ
- T1 Tumor confined to region of origin with normal mobility
- T2 Tumor involves adjacent supraglottic site(s) or glottis without fixation
- T3 Tumor limited to larynx with fixation and/or extension to involve postcricoid area, medial wall of pyriform sinus, or pre-epiglottic space.
- T4 Massive tumor extending beyond the larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage.

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Maxillary Sinus

- T1 Tumor confined to the antral mucosa of the infrastructure with no bone erosion or destruction.
- T2 Tumor confined to the suprastructure mucosa without bone destruction, or to the infrastructure with destruction of medial or inferior bony walls only.
- T3 More extensive tumor invading skin of cheek, orbit, anterior ethmoid sinuses, or ptergoid muscle.
- T4 Massive tumor with invasion of cribiform plate, posterior ethmoids, sphenoid, nasopharynx, pterygoid plates, or base of skull.

Nodal Involvement (N)

- NX Nodes cannot be assessed
- N0 No clinically positive node
- 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 cm 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 Metastasis (M)

- MX Not assessed
- M0 No (known) distant metastasis
- M1 Distant metastasis present
Specify

Specify sites according to the following notations:

Pulmonary	-	PUL
Osseous	-	OSS
Hepatic	-	HEP
Brain	-	BRA
Lymph Nodes	-	LYM
Bone Marrow	-	MAR
Pleura	-	PLE
Skin	-	SKI
Eye	-	EYE
Other	-	OTH

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Stage Groupings

Stage I	T1 NO MO
Stage II	T2 NO MO
Stage III	T3 NO MO
	T1 or T2 or T3, N1, MO
Stage IV	T4, NO or N1, MO
	Any T, N2 or N3, MO
	Any T, any N, M1

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

- 100 Normal; no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease.
- 80 Normal activity with effort; some sign or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most personal needs.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospitalization is indicated, although death not imminent.
- 20 Very sick; hospitalization necessary; active support treatment is necessary.
- 10 Moribund; fatal processes progressing rapidly.
- 0 Dead.

APPENDIX III
MANAGEMENT OF DENTAL PROBLEMS
IN IRRADIATED PATIENTS¹

DENTAL CARE FOR IRRADIATED PATIENTS

Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

PREIRRADIATION CARE AND PROCEDURES

The patients may be grouped into 4 groups in accordance with the problems they present prior to irradiation.

GROUP 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

GROUP 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

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1. Daly, Thomas E.: Management of Dental Problems in Irradiated Patients. The Radiological Society of North America. Chicago, Illinois., November 29-30, 1971.

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GROUP 3

Includes those in whom dental condition is fair, including those patients whose teeth are restorable by ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in close proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examination should show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth which are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

GROUP 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion and in which few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom-made fluoride carriers.

EXTRACTION OF TEETH

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that primary closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

CAUSATIVE FACTORS

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduction of pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed and those teeth with large amounts of plaque formation present. Doses of radiation in excess of 2,000 cGy to salivary tissue place the teeth at risk.

PREVENTIVE PROGRAM

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is

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"Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products Corp., both of which are available through local dental supply houses. This material is moulded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up care is necessary.

RESULTS

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Group 3 and 5 patients randomized with and without fluoride treatment showed reduction in radiation caries 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

FAILURE TO CONTROL DECAY

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

HYPERSENSITIVITY OF TEETH

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment for 10 to 15 minutes 3 times a day is recommended.

INFECTIONS

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

BONE NECROSIS

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons, including: impairment of normal metabolism, increased susceptibility to infection, and severely limited repair process. Bone

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necrosis occurs most often after post-irradiation surgery or other traumas. Conservative management should be tried first, though in the more aggressive lesions a more radical approach may ultimately be necessary.

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APPENDIX IV

SAMPLE CONSENT FORM*

TREATMENT TITLE: "Fast Neutron Irradiation for Treatment of Advanced Head and Neck Cancer"

1. _____ Patient's name _____ Patient's Number

2. PURPOSE OF STUDY: Routine (conventional) radiation therapy, produced by radioactive cobalt or linear accelerators, is unsatisfactory in patients with advanced head and neck tumors. Better results have been reported from England using a new type of radiation called neutrons. Neutron therapy has been tried in the U.S. in a few facilities for the past 10 years. Thus far, the results have been about the same as those achieved with conventional radiotherapy. However, the schedule in which the neutron therapy was administered was different from the one used in England.

In the present study, investigators will try to achieve the superior results as in the English trial by adhering to the same treatment schedule.

3. DESCRIPTION OF TREATMENT/PROCEDURE: Neutron radiation will be used to treat the tumor and adjacent area. Conventional radiation such as that produced by a linear accelerator will be used to treat areas which are adjacent to the tumor in order to prevent tumor spreading to these areas.

4. SIDE EFFECTS: Are the same as with conventional radiation therapy and depend on the area treated. During treatment and immediately after, you will develop redness of the skin and hair loss in the area treated, dryness of the mouth and soreness of the throat. Later, more severe problems may occur in up to 20% of the patients. They include mucosal ulcers, chronic damage to the jaw, tooth decay and, very rarely, paralysis due to spinal cord damage. Every precaution will be taken to avoid the possibility of spinal cord damage and the other possible side effects mentioned.

5. POTENTIAL BENEFITS: This treatment may be more effective in controlling your tumor than other forms of treatment.

6. ALTERNATE TREATMENTS: Conventional radiation therapy alone or in combination with chemotherapy drugs may be used.

I have been given an opportunity to ask any questions concerning the treatment involved and my doctors have been willing to answer. I hereby authorize Dr. _____, the attending physician/investigator and/or the physician/investigator he may designate, to administer the treatment.

*Sample Consent Form submitted by the Study Chairman

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8. I have been told and understand that I am able to withdraw my consent and to stop my participation in this study at any time, and that such withdrawal of consent or discontinuation will not prejudice my physician against me.
9. I have been assured that my confidentiality will be preserved and that names of patients will not be revealed in any reports or publications resulting from this study.
10. I have been informed that should I suffer any physical injury as a result of participation in this research activity, all of the necessary medical facilities are available for treatment, in so far as is reasonably possible. I understand, however, that I cannot expect to receive any payment for hospital expenses or any financial compensation for such injury.
11. I understand that my hospital records may be inspected by representatives of RTOG or NCI in accordance with established policies for monitoring clinical trials.
12. With full knowledge of this, I voluntarily consent to receive the above treatment.

Name of Patient	Date
Witness	Patient or Person Responsible
Witness	Relationship

12. I have discussed this project with the subject and/or his authorized representative using a language which is understandable and appropriate. I believe that I have fully informed this patient of the nature of this study and its possible benefits and risks.

Physician/Investigator

Date

ACUTE RADIATION EFFECTS

EARLY: ORGAN/TISSUE	0 (NORMAL)	1 (MILD)	2 (MODERATE)	3 (SEVERE)	4 (LIFE THREATENING)	*5
Skin	Normal	Mild erythema, pigmentation, partial epilation, pruritis, dry desquamation, decreased sweating.	Brisk erythema, limited moist desquamation, no pain, complete epilation.	Confluent moist desquamation associated with pain.	Necrosis, ulceration, hemorrhage. Rx requires hospitalization.	
Subcutaneous Tissue	Normal	Erythema, mild to moderate edema, pigmentation.	Severe edema.	Healing ulceration.	Non-healing ulceration, necrosis, Rx requires hospitalization.	
Mucous Membrane	Normal	Erythema.	Brisk erythema, patchy mucositis.	Confluent fibrinous mucositis, ulceration, limited necrosis (< 2 cm ²), occasional limited bleeding.	Extensive necrosis (> 2 cm ²), hemorrhage requiring hospitalization.	
Salivary Glands	Normal	Minimal swelling, slight tenderness, detectable decrease in saliva.	Painful swelling, thick saliva, dry mouth.	Xerostomia requires intubation, hyperalimentation.	Xerostomia requires gastrotomy or hospitalization.	

*5 - Any reaction which caused the death of the individual

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