

RADIATION THERAPY ONCOLOGY GROUP

RTOG 76-10

PROTOCOL TO STUDY

NEUTRON THERAPY IN THE TREATMENT OF
SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY, PHARYNX AND LARYNX
USING RADIATION THERAPY AS THE ONLY PLANNED TREATMENT MODALITY

Closed

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RADIATION THERAPY ONCOLOGY GROUP

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PROTOCOL FOR NEUTRON THERAPY FOR CARCINOMA OF THE HEAD & NECK REGION
PATIENTS TO BE TREATED WITH RADIATION THERAPY ONLY

SCHEMA

Stratify:

Region		
Oral Cavity/Oropharynx	R	A. Photons (6600-7400 rad/7-8 wks)
Hypopharynx	A	B. Mixed (3 photons, 2 neutrons fx/wk) 4500 photons + neutrons (ranging from 900 rad Fermi to 730 rad Seattle) 7-8 weeks*
Supraglottic Larynx	N	
	D	C. Neutrons (2400 rad Fermi to 1950 rad Seattle)7-8 wks 3-4 fx/wk**
Extent of Primary	O	
T ₂ , T ₃ /T ₄	M	
	I	
	Z	
	E	

Neutron Facility

1. Reduced fields at 4400-5000 rad eq. (using: neutrons x equivalency factor) whenever possible. Treat lower neck with only photons.
 2. Photons 180-200 rad/fraction.
- * At least 30% of total dose with neutrons to primary tumor volume using: neutrons x equivalency factor (E.F.)/(n x E.F.) + photons.
- ** At least 90% of total dose with neutrons.

A facility may choose to randomize patients into two or three arms but all must select arm A. Geographic subsets may be selected within a facility. Facilities may decide not to include certain specific regions, sites or T & N classifications within sites.

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INTRODUCTION

1.1 Rationale for Combined Neutron & Photon Radiotherapy.

In the past 25 years, advances in the field of radiotherapy have resulted in a substantial improvement in local control, while the incidence of normal tissue complications has declined. Nevertheless, a significant number of tumors continue to be locally incurable at doses within tissue tolerance, and improved control rates are achieved only at the cost of increased radiation sequelae. In the management of human cancer, both the duration and quality of survival are important. Fast neutrons have been proposed as a means of improving the control of bulky tumors while keeping radiation injury to a minimum.

The principal rationale for fast neutron radiotherapy is related to the hypoxic cell problem. Numerous radiobiological studies have shown that hypoxic cells are 2.5 to 3.0 times (OER*) more resistant to the effects of conventional X and gamma irradiation than are well oxygenated cells. While the cells in most normal tissues are well oxygenated, most solid tumors have hypoxic regions which have outgrown their vascular supply. It has been postulated that these cells remain viable and provide a focus for local recurrence. With neutrons, radiosensitivity is less dependent upon the state of oxygenation.

Doses of 6000-7000 rad are required to achieve even modest control rates of extensive carcinomas. Fast neutron doses equivalent to 6000-7000 rad may result in significant subcutaneous fibrosis with some risk of major complications. Any radiobiological advantage of fast neutron beams might

*Oxygen enhancement ratio (OER) refers to the ratio of the radiation dose required to produce a specified biologic effect under anoxic conditions to the dose required to produce the same effect under well oxygenated conditions.

masked by the poor dose distribution. This protocol, therefore, uses a mixed beam of neutrons and high energy photons in one arm in an attempt to improve the radiation dose distribution and hopefully improve the local control rate while decreasing the potential for complications. The objectives are: 1) to take advantage of the radiobiological properties of neutrons by irradiating with neutrons twice weekly throughout the course of treatment; and 2) to take advantage of the dose distribution properties of high energy photons by irradiating with photons three times weekly. In this manner the study will use conventional five times weekly fractionation in this treatment arm. Because low LET radiation has a good control rate for subclinical disease and because hypoxic cells are most numerous in the gross tumor volume, the neutron dose will be limited to areas of gross tumor with a modest margin.

1.2 Neutron Therapy Equipment.

The neutron beam shall have such a penetrating power that for a 10 x 10 cm field in depth at which the maximum dose per monitoring unit is reduced to half of its value is 9.0 cm or greater as measured in tissue equivalent fluid at the standard SAD or SSD used at the institution.

1.3 Scope of the Problem.

It is generally agreed that patients with advanced (T_3 and T_4) squamous cell carcinoma of the upper air and food passages have a poor prognosis as far as both local control and ultimate survival are concerned. This applies whether they are treated by surgery or by radiation therapy. A report to the Medical Research Council (England) on the first results of a randomized clinical trial of fast neutrons compared with x- or gamma rays in the treatment of advanced tumors of the head and neck, presented by Mary Catterall, Ian Sutherland, and David K. Bewley (1) showed that in 37 out of 52 persons treated with neutrons and in 16 out of 50 patients treated with photons the local tumor regressed completely. The tumor later recurred in 9 of the 16 photon treated patients, but in

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none of the 37 neutron treated patients. These advantages to the neutron treated patients were statistically highly significant. Complications after treatment did not differ significantly between the two groups but despite these differences in local control there was no significant difference in survival between the two series, suggesting that local failure may be associated with a failure of host resistance and general dissemination. There is clearly need to confirm these findings, to compare optimal neutron beam therapy with the best available conventional photon beam therapy executed according to the highest standards of current practice and to optimize the procedure with both photons, neutrons, mixed beam, and combinations of any of these with surgery.

The patients considered for this protocol will be cases in which the surgeons consider the patient to be inoperable because of the extent of the primary tumor or for medical reasons, or those cases in which the institutional policy is to treat using radiation therapy alone.

This protocol is designed to randomly allocate patients referred for radiation therapy to one of three treatment arms. These are: 1) treatment with neutron radiation therapy only; 2) photon radiation therapy only; 3) a mixed beam consisting of three fractions per week using photons and two fractions using neutrons.

The irradiated group will be evaluated at an appropriate time to assess response so as to permit surgical rescue of failures in this category. The clinical impression of residual disease at 90 to 120 days after initiation of radiation will be accepted as indicating that these lesions will not be cured by the radiation alone. Patients in this category will be treated surgically and will count as failures insofar as the treatment with radiation therapy is concerned. However, the

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results of this policy will be evaluated as it may well prove to be one of the more successful approaches in management, even of recurrent cases.

2.0 OBJECTIVES

2.1 Assessment will be made of primary endpoints.

- 2.1.1 Local Control. Absence of persistent or recurrent disease. Note: Persistent disease is characterized by failure of local tumor to be eradicated as evidenced by clinical or biopsy finding of tumor at primary site after completion of treatment. Recurrent disease implies complete tumor clearance at local site followed by reappearance of tumor locally. Assessment of local control will be made by:
- 2.1.1.1 Clinical absence of local disease.
 - 2.1.1.2 Biopsy-proven evidence of recurrence.
- 2.1.2 Length of survival and tumor and functional status at time of death.
- 2.1.3 Complications due to diverse forms of therapy.
- 2.1.4 Assessment of rehabilitation and functional status post therapy. The Karnofsky scale will be used.

3.0 SELECTION OF PATIENTS

3.1 Eligibility Criteria.

Initially the patients considered for the study will be drawn from a group consisting of all patients with squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx who are considered for treatment using only radiation therapy.

- 3.1.1 Eligible patients will have a previously untreated primary neoplasm.
- 3.1.2 Patients who have had malignant disease previously, but at a site other than the head and neck, and have been disease-free for 5 years are also eligible.

3.1.3 Patients with tumors originating in the following regions and sites will be admitted to the study:

<u>Region</u>	<u>Site</u>
1. Oral Cavity	1. Oral Tongue (anterior 2/3) 2. Floor of Mouth 3. Buccal Mucosa 4. Lower Gingiva (Alveolar Ridge) 5. Retromolar Gingiva
2. Oropharynx	1. Faucial Arch (post. pillar, soft palate) 2. Tonsillar Fossa and tonsil 3. Base of tongue (glossoepiglottic and pharyngoepiglottic folds) 4. Pharyngeal wall (lateral and posterior wall, posterior tonsillar pillar)
3. Hypopharynx	1. Pyriform Sinus 2. Postcricoid Area 3. Posterior Pharyngeal Wall
4. Supraglottic Larynx	1. Ventricular Bands (false cords) 2. Arytenoids 3. Suprahyoid Epiglottis 4. Infrahyoid Epiglottis 5. Aryepiglottic Fold

3.1.4 The primary lesions must be T₂, T₃ or T₄ with nodes of any N staging (see Appendix I).

3.2 Ineligibility Criteria.

Patients are eliminated from the study for the following reasons:

3.2.1 Tumor is classified as T₁ with nodes of any N staging.

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- 3.2.2 Patients with distant metastases.
- 3.2.3 Patients with two simultaneous tumors in the region under study.
- 3.2.4 Patients who had previous chemotherapy for malignant tumor, or previous radical surgery or radiation therapy of the head and neck, except skin cancer.
- 3.2.5 General medical reasons.
 - 3.2.5.1 Poor general condition indicated by a Karnofsky performance status equal to or less than 50 (e.g., severe malnutrition, below 60% standard weight) not itemized below, which in the investigator's opinion precludes any curative effort.
- 3.2.6 Exclusions.
 - 3.2.6.1 A facility may decide not to include certain specific regions, sites, or T & N classifications within sites in the study. Similarly, specific clinics or groups of referring physicians may not wish to participate. Such selective actions (or geographic subsets) will be permitted, provided they are stated before activation of the protocol at the facility and provided they remain in force throughout the study.
 - 3.2.6.2 A facility (or geographic subset within a facility) may choose to participate in two or three of the treatment randomizations, but all must include A. - Photons only.

4.0 STAGING WORK-UP

- 4.1 In addition to history and physical examination, appropriate diagnostic studies will be used to evaluate the extent of the primary tumor.
 - 4.1.1 Draw appropriate diagrams of the primary tumor and cervical nodes with accurate measurements of dimensions of the lesions. Appropriate diagrams are provided by the RTOG Operations Headquarters.

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- 4.1.2 An assessment of the patient's performance status using the Karnofsky Scale (Appendix IV).
- 4.2 Chest x-ray.
- 4.3 The staging according to the AJC T & N classification (see Appendix I).
- 4.4 Laboratory Studies.
 - 4.4.1 Hemoglobin or hematocrit, WBC, differential and platelets.
 - 4.4.2 Serology, positive serology will not exclude a patient, but such knowledge will be valuable in determining retrospectively whether patients with positive serology respond less well because of impaired vascularity.
 - 4.4.3 Other laboratory tests as indicated by the clinical condition of the patient.
- 4.5 Endoscopic procedures should be performed as required.
 - 4.5.1 Satisfactory biopsy of the primary is required.
 - 4.5.2 Needle biopsy of metastatic nodes is desirable.
- 4.6 Dental care (see Appendix III) to be complete.

5.0 RANDOMIZATION

- 5.1 Patients will be stratified according to the following factors:
 - 5.1.1 Region of the primary.
 - 5.1.2 Extent of the primary tumor (T stage).
 - 5.1.3 Institution.
- 5.2 Call Operation Headquarters for randomization (215-574-3191) between 9:00 a.m. and 5:00 p.m., ET, Monday-Friday. The following will be required:
 - 5.2.1 principal investigator's name
 - 5.2.2 protocol
 - 5.2.3 institution
 - 5.2.4 patient's name
 - 5.2.5 region of tumor (oral cavity, oropharynx, hypopharynx, or supraglottic larynx)
 - 5.2.6 T classification

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5.2.7 Geographic subset (if these have been indicated by a facility)

The Operation Headquarters Office will give the treatment assignment and the project case number. The randomization will be confirmed by mail.

5.3 Treatment by radiation therapy should begin within 14 days after randomization.

6.0 RADIATION THERAPY

6.1 Equipment.

6.1.1 Photons. Photon irradiation will be delivered using radiation therapy equipment operating at 4.0 MeV or greater or Cobalt 60 with a minimum SSD of 80 cm or 80 cm to axis for SAD techniques.

6.1.2 Neutrons. The neutron beam will meet the specifications stated in 1.2.

6.2 Localization Requirements and Documentation.

Localization films and the radiotherapy treatment prescription must be submitted to RTOG Headquarters within 7 days of randomization. At the completion of therapy, the radiotherapy flow sheets, copies of the boost localization films and isodose distributions should be submitted with the RTOG treatment summary forms.

6.3 Target Volume.

6.3.1 Primary Target Volume. In general, the primary target volume will consist of the primary tumor and clinically positive lymph nodes with a safety margin of 2 cm (allowing for sensitive normal structures). It should exclude the spinal cord.

6.3.2 Secondary Target Volume. The secondary (low dose) target volume will include the supraclavicular nodes, without unnecessary irradiation of the shoulder, and the lower cervical nodes.

6.4 Treatment Planning.

In general, the primary target volume will be treated with parallel opposed fields in which the posterior limit of the

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beam in the reduced (boosted) volume lies anterior to the spinal cord, or where this is not adequate to cover all macroscopic disease, beams should be angulated so that the treatment volume (isodose contour encompassing the planned target volume) excludes the spinal cord.

The secondary target volume will generally be irradiated with a single, anterior field (with a midline block) which abuts the lower border of the fields for the primary target volume at the skin surface.

Alternative treatment techniques may be used as long as the primary and secondary target volumes are irradiated to the doses specified in section 6.5.

6.5 Dose Definitions and Schedule.

6.5.1 Equivalency Factors. Since pre-clinical RBE estimates for a given high-LET installation vary widely depending on dosage and the biological end point studied, it is not possible to define a clinical RBE which will be valid under all circumstances. It is preferable to define an "equivalency factor" as the best average for the RBE determined for neutron doses compared with conventionally fractionated photon equivalents (individual photon doses equal to or less than 200 rad). In effecting this comparison, neutron doses are conventionally expressed as total absorbed dose which includes a gamma-component of about 7%. Under these conditions equivalency factors for the range of neutron energies in this program are as follows:

Fermilab	= 3.0
Tamvec	= 3.2
Manta/Glanta	= 3.3
Seattle/Chicago	= 3.7

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6.5.2 Primary Target Volume Doses.

6.5.2.1 Neutron Therapy. Neutron beam therapy will be given at a sequence of 3 or 4 fractions per week spaced in any convenient manner. At least 90% of the total dose delivered will be with neutrons (remaining 10% may be accounted for by delivery of some treatment with conventional equipment to allow for unscheduled technical problems at the neutron facilities). Target absorbed doses delivered in 7 to 8 weeks, (range \pm 100 rad) of:

Fermilab	2400 rad
Tamvec	2100 rad
Glanta	2140 rad
Seattle/Chicago	1900 rad

6.5.2.2 "Mixed Beam" Therapy. The mixed beam procedure will consist of 3 fractions of photons plus 2 fractions of neutrons each week. At least 30% and not more than 50% of the total dose delivered using the formula

$$\frac{\text{neutron dose (n) x equivalency factor (E.F.)}{n \times \text{E.F.} + \text{photon dose}}$$

will be with neutrons. A total target dose equivalent to a photon dose between 6600 and 7400 rad will be delivered in 35 to 40 fractions given in 7 to 8 weeks. The neutron contribution to this equivalent dose will be calculated on the basis of the equivalency factors listed in 6.5 above. In general, this will consist of 4000-4400 rad of photons and the following doses of neutrons:

Fermilab	850-1000 rad
Tamvec	800-950 rad
Glanta	765-920 rad
Seattle/Chicago	750-900 rad

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- 6.5.2.3 Photon Beam. A total target absorbed dose of 6600 to 7400 rad will be delivered in 35 to 40 fractions given over 7 to 8 weeks. Daily fractionation (5 per week) of 180 to 200 rad will be used at all times.
- 6.5.3 Secondary Target Volume Dose. 4500 to 5000 rad with photons or the equivalent with neutrons (ranging from 1500 to 1600 rad at Fermilab to 1250 to 1350 neutron rad at Seattle) at D maximum should be delivered to the uninvolved neck area. Treatment fields may then be reduced to include only macroscopic disease, and treatment continued to the reduced volume up to the total doses described. With the mixed beam and photon beam options 4500 rad (photons) should be given to uninvolved neck areas.
- 6.5.4 Dose Uniformity in the Primary Target Volume. Dose gradients within the primary target volume may range from 7-1/2% below to 7-1/2% above the target absorbed dose. Whenever possible, the dose in the target volume should be kept within 5% of the prescribed target absorbed dose.
- 6.5.5 Dose/time Modifications. A continuous course should be maintained if at all possible, but if the radiation reaction requires an interruption of therapy, a maximum 14-day single rest will be permitted. This time will be added to the overall time specified.
- 6.6 Brachytherapy. Patients assigned to receive either "mixed beam" irradiation (as in 6.5.2.2) or photon irradiation (as in 6.5.2.3), may, with suitable lesions, have external radiation terminated at a midplane dose of 5000 rad (or 5000 rad equivalent) and have radiotherapy completed using an interstitial implant delivering a dose of 3000 rad in 3-4 days calculated at the periphery of the boosted volume, or as the minimum isodose which encompasses the tumor volume.

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6.7 Maximum Dose to Critical Structures.

The spinal cord dose should not exceed 5000 rad/5 weeks with photons or the equivalent with "mixed" beam or neutrons based on the formula: $D + 4 D_n \leq 5000$ rad.

7.0 STUDY PARAMETERS AND FOLLOW-UP

7.1	Pre-Study	Month														
		3,6,9,12,15,18,21,24,30,36,42,48,54,60														
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CBC, Platelets	x															
Serology	x															
Liver Function	x															
Chest x-ray	x	x	x		x		x		x		x		x		x	
Photograph of treated area		x	x				x		x		x		x		x	

7.2 Follow-Up

- 7.2.1 Follow-up examinations will be reported at 3 monthly intervals starting with day 90 (day 1 being the first day of treatment) for 2 years and at 6 monthly intervals for the subsequent 3 years, giving a total follow-up period of 5 years (Form 4).
- 7.2.2 If the patient's tumor is judged to be residual or recurrent at the primary site on day 90 to 120, from initiation of the treatment then radical surgery should proceed if feasible.
- 7.2.3 Follow-up examination will include an assessment of the patient's rehabilitation and functional status post therapy.
- 7.2.4 Follow-up data will include an assessment of late complications.

7.3 Measurements of Specific Endpoints.

Criteria of response shall be measured as follows:

7.3.1 Local Response. The rate of regression of the primary tumor under radiotherapy will be determined by measurement of the primary tumor in maximum dimensions and dimensions at right angles to it, if possible; otherwise by subjective assessment of percentage regression. At day 90 to 120, local assessment shall include, but not be limited to:

7.3.1.1 A complete regression of tumor, i.e., total disappearance of tumor mass without residual induration.

7.3.1.2 Residual induration, if no tumor is seen but induration still can be felt in the area of the primary tumor.

7.3.1.3 Residual tumor when this is apparent on clinical examination or by biopsy.

7.3.2 Status of Neck. Weekly measurements should be made during the course of therapy, if possible, or subjective assessment of percentage regression. At day 90 to 120 an assessment should be made including:

7.3.2.1 No evidence of node enlargement in the neck.

7.3.2.2 Residual induration in the neck.

7.3.3 Presence or absence of metastases by clinical evaluation of appropriate study.

7.3.3.1 Chest x-ray, liver function tests, bone scan, or surveys, etc.

7.3.4 Rehabilitation of the Patient. Ongoing data recorded at all follow-up examinations shall contain criteria with regard to:

7.3.4.1 Xerostomia, loss of taste sense

7.3.4.2 Local pain

7.3.4.3 Fibrosis in the treated region, both primary and neck.

- 7.3.4.4 Evidence of soft tissue necrosis.
- 7.3.4.5 Evidence of bone necrosis.
- 7.3.4.6 Skin changes in the treated area.
- 7.3.4.7 Restricted joint movement, trismus.
- 7.3.5 Evidence of rehabilitation and Swallowing Function as to:
 - 7.3.5.1 Ability to eat solid foods or soft foods and to swallow liquids normally.
 - 7.3.5.2 Recovery of normal speech in the absence of laryngectomy.
 - 7.3.5.3 Esophageal speech in laryngectomized patients.
- 7.3.6 Performance status using the Karnofsky Scale (Appendix IV).
- 7.3.7 Late normal tissue reactions should be recorded at the time of each follow-up according to the scale in Appendix V.
- 7.3.8 A patient's death shall be reported on the death form. Post mortem examination of the irradiated region is highly desirable.

8.0 STATISTICAL CONSIDERATIONS

In projecting the number of patients required for this study the following assumptions have been made:

- a) The main treatment comparison will be between the mixed modality and photon only arms.
- b) That the two year survival rate following photon irradiation is currently approximately 35% while the percentage of patients whose disease is controlled locally is of the same order of magnitude.
- c) That an increase, by 20% to 55% of two year local control rate using neutron therapy is desirable, and that if such an improvement is possible that it be detected with high probability (greater than or equal to 85%) using a significance level (one-sided) of $p=0.05$.

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d) That the participating institutions will contribute a total of approximately 40 patients per year to the treatment comparison mentioned in assumption "a".

Based on these assumptions the study should require about 2 to 2-1/2 years of patient accession in order to accumulate the 70 to 80 patients per arm required to meet the above objectives.

As the study progresses, these estimates are subject to revision.

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REFERENCES

1. British Medical Journal, June 21, 1979

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APPENDIX I

STAGING OF CANCER AT HEAD AND NECK SITES

American Joint Committee for Cancer Staging and End Results Reporting
(1977)

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
T0 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
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

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- 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

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

Primary Tumor (T)

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

Oropharynx:

- 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 tissues of neck, or root (deep musculature) of tongue

Hypopharynx:

- 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

Supraglottis - Ventricular bands (false cords)

- Arytenoids
- Epiglottis (both lingual and laryngeal aspects)
 - Suprahyoid epiglottis
 - Infrahyoid epiglottis
 - Aryepiglottic folds

Supraglottis:

- TIS Carcinoma in situ
- T1 Tumor confined to region or origin with normal mobility
- T2 Tumor involves adjacent supraglottis 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.

Nodal Involvement (N)

- NX Nodes cannot be assessed
- NO No clinically positive nodes
- N1 Single clinically positive homolateral node less than 3 cm in diameter
- N2 Single clinically positive homolateral nodes 3 to 6 cm in diameter, or multiple clinically positive homolateral nodes, none over 6 cm in diameter
- N2a Single clinically positive homolateral node 3 to 6 cm in diameter.

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- N2b Multiple clinically positive homolateral nodes, none over 6 cm in diameter.
- N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s)
 - N3a Clinically positive homolateral node(s), over 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 _____

APPENDIX II

PATHOLOGY

The lesion must be an epidermoid carcinoma. The term "transitional cell" is to be avoided. Lymphoepithelioma will be included and placed in a separate category. In addition to his own microscopic description and diagnosis, the pathologist is requested to use one or more of the following three designations: low-grade (well-differentiated), intermediate (moderately differentiated), high-grade (undifferentiated).

The consultant pathologist is available to provide uniformity of opinion for this study.

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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.

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

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 3mm 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 one half of the bone still present around root surfaces. These patients require removal of any teeth which are non-salvageable in accordance with the above. 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 that 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 rad to the 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 concentration on the tooth surface

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and by the effect of 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 using casts. Material used for making a mouth guard is "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 use of the carrier. This will be continued for an indefinite period of time. Close follow-up care is necessary.

RESULTS

In the 5½ 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 Group 4 patients randomized with and without fluoride treatment showed reduction in radiation caries from 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 the 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 during 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 a severely limited repair process. Bone 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.

APPENDIX IV

KARNOFSKY PERFORMANCE STATUS

- 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 process progressing rapidly.
- 0 Dead.

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Appendix V

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Organ/Tissue	0	1 Mild	2 Moderate	3 Severe	4 Life Threatening	5*
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patchy atrophy Moderate telangiectasia Total hair loss	Marked atrophy Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture (< 10% linear reduction)	Severe induration and loss of subcutaneous tissue Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANES	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucus	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness Poor response on stimulation	Complete dryness No response on stimulation	Necrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono or para quadriplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headache Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or Paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panophthalmitis Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever. Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency Continuous oxygen Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion and ST changes Sinus tachycardia > 110 (at rest)	Moderate angina of effort Mild pericarditis Normal heart size Persistent abnormality T wave and ST changes Low QRS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade Severe heart failure Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilatation required	Necrosis Perforation, Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping. Bowel movement < 5 times daily. Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement > 5 times daily. Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation, Fistula	
LIVER	None	Mild lassitude, nausea dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis Hepatic coma or Encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine Clearance > 75%	Persistent moderate albuminuria (2+) Mild hypertension. No related anemia. Moderate impairment renal function Urea > 36-60 mg% Creatinine 2.5-4.0 mg% Creatinine Clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (< 10g%) Severe renal failure Urea > 60 mg% Creatinine > 4.0 mg% Creatinine Clearance < 50%	Malignant hypertension Uremic coma Urea > 100 mg%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity (< 150 cc)	Necrosis Contracted Bladder (capacity < 100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Retardation of growth Irregular bone sclerosis	Severe pain or tenderness Complete arrest bone growth Dense bone sclerosis	Necrosis Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis Complete fixation	