RTOG 76-09

RADIATION THERAPY ONCOLOGY GROUP

PROTOCOL TO STUDY

NEUTRON THERAPY IN THE TREATMENT OF

POTENTIALLY OPERABLE PATIENTS WITH

SQUAMOUS-CELL CARCINOMA OF THE ORAL CAVITY, PHARYNX, AND LARYNX

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Stratify:

Region:
- Oral Cavity
- Oropharynx
- Hypopharynx
- Supraglottic Larynx

RANDOMIZE

~~A. Mixed (3 photons, 2 neutrons fractions/week) 4500 photons + neutrons (ranging from 900 rad Fermi to 730 rad Seattle)/7-8 weeks**~~ not a CTF option

B. Mixed** + surgery

C. Photons + surgery

Extent of Primary
T_2, T_3, T_4

Surgery
Planned
Performed

Institution
T_2, T_3, T_4 and any N except N_3A

1. Photons 180-200 rad/fraction. 5 fractions/week.

2. In options B and C radiotherapy may be given prior to or following surgery. Doses are 5000 rad photons or 1350-1600 rad neutrons/5-5 1/2 weeks. If radiotherapy is delivered postoperatively, a 1000 rad photon or 250-350 rad neutron boost should be delivered to the region of the primary.

** At least 30% of total dose with neutrons to primary target volume using: neutrons x equivalency factor (E.F.)/(N x E.F) + photons

A facility may choose to randomize patients into two or three treatments, but all must include option C.

Geographical subsets within a facility may choose separate options.

A facility can choose to exclude specific regions, sites, or T and N classifications.

1.0 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. A significant number of tumors, neverthe'ess, 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 oxygen enhancement ratio (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.

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*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.

Although fast neutrons are theoretically superior to photons radiobiologically, the physical properties of neutron beams are significantly inferior to those of high-energy photon beams:

1) Poor skin sparing and depth dose - The dosimetric properties of the clinical neutron beams are compared with those of high-energy photon beams in Table I. The depth dose and skin paring qualities of the most energetic neutron beams are approximately the same as those of ^{60}Co.
2) Horizontal beam - All current neutron facilities use a horizontal beam.
3) Increased absorption in fat - Bewley (1) has shown that fat absorbs approximately 18% more energy with neutrons than water-density tissue. These calculations have been confirmed by measurements at TAMVEC. This factor could lead to increased subcutaneous fibrosis.

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 and a high risk of major complications. Consequently, any radiobiological advantage of fast-neutron beams might be 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 ultimately to 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.

TABLE I.

	Neutrons (Deuteron energy--MeV)				Photons		
	16	21.5	35	50	60Co	10 MeV	25 MeV
Depth of D_{max} (cm) (10x10 cm Fld)	.2	.3	.5	1.0	.5	2.4	3.9
Depth of 50% dose (cm)	8.3	9.6	12.1	13.0	11.4	18.	22.

1.2 Neutron Therapy Equipment.

The neutron beam shall have such a penetrating power that for a 10 x 10 cm field the 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. The Radiation Therapy Oncology Group has a currently active protocol (73-03), in which patients with squamous carcinoma of the head and neck region are randomly assigned to receive only radiation (oral cavity and oropharynx regions) or surgery combined with radiation either pre- or postoperatively (also randomly assigned). Preliminary results of the study with regard to local control do not demonstrate any difference among the treatment assignments. Data from this protocol will add to the information being obtained in Protocol 73-03.

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 (2) 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 16 photon-treated patients, but in 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 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 combination of any of these with surgery.

Squamous carcinoma arising in the oral cavity, oropharynx, hypopharynx, and supraglottic larynx are appropriate for study. Where the disease is operable (T_2, T_3, and T_4) there is need to compare results with definitive radiation therapy alone (neutrons or mixed beam) with those of surgery supplemented with pre- or postoperative radiation using either neutrons or conventional low-LET beams.

This protocol is designed to randomly allocate patients between radiation therapy only, using one of two treatment schemes involving neutrons, or a combination of surgery and radiation therapy. The treatment arm of pre- or postoperative photon radiation (5000 rad in 5-5 1/2 weeksto 6000 rad in 6-6 1/2

weeks) is identical to the current RTOG study (RTOG 73-03) and may permit some comparisons between the two studies. The groups assigned to receive only radiation therapy would have to 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 radiation alone. Patients in this category will be treated surgically and will count as nonsuccesses insofar as the treatment with radiation therapy alone is concerned.

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

2.0 OBJECTIVES

2.1 To determine if mixed beam radiation either alone or combined with surgery results in improved local tumor control as compared to photon radiation combined with surgery.

2.2 Assess length of survival and functional status for each treatment.

2.3 Determine complications due to diverse forms of therapy.

2.4 Assess 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, in which a combination of radiation therapy and surgery is acceptable management in the institutions.

3.1.1 Eligible patients who have had 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:

Region	Site
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 T_2, T_3, or T_4 with nodes of any N staging, except N_3A (see Appendix 1).

3.2 Ineligibility Criteria.

Patients are eliminated from the study for the following reasons:

3.2.1 Tumor is classified as T_1 with nodes of any N staging.

3.2.2 Patients with nodes stage N_3A.

3.2.3 Patients with distant metastases.

3.2.4 Patients with two simultaneous tumors in the region under study.

3.2.5 Patients who had previous chemotherapy for malignant tumor, or previous radical surgery or radiation therapy of the head and neck, except for skin cancer.

3.2.6 General Medical Reasons.

3.2.6.1 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. In addition, where appropriate laboratory tests indicated abnormalities as follows:

3.2.6.2 Total plasma proteins below 5 g/100 ml or other severely abnormal liver function tests, such as SGOT, alkaline phosphatase, etc.

3.2.7 Exclusions.

3.2.7.1 A facility can choose to exclude specific regions, sites, or T and N classifications within sites for randomization for the entire facility, specific clinics, or specific groups of referring physicians. These exclusions (or geographic subsets) must be reported prior to activation of the protocol at the facility.

3.2.7.2 A facility (or geographic subset within a facility) may choose to participate in two, three, or four of the treatment randomizations, but all must include C.-Photons + surgery.

4.0 STAGING WORK-UP

4.1 In addition to a 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 Operation Headquarters.

4.1.2 An assessment of the patient's performance status using the Karnofsky Scale (see Appendix IV).

4.2 Chest X-ray.

4.3 The staging of T and N classification according to the American Joint Committee (see Appendix I).

4.4 Laboratory Studies.

4.4.1 Hemoglobin or hematocrit, WBC, differential and platelets.

4.4.2 Liver function studies; at least two of the following - total bilirubin, SGOT, SGPT, alkaline phosphatase.

4.4.3 Serology; positive serology will exclude a patient, but such knowledge will be valuable in determining retrospectively whether patients with positive serology respond less well because of impaired vascularity.

4.4.4 Other laboratory tests as indicated by the clinical condition of the patient.

4.5 Nuclear medicine studies: a liver scan may be used as a substitute for one of the liver function studies.

4.6 Endoscopic procedure should be performed as required.

4.6.1 Satisfactory biopsy of the primary is required.

4.6.2 Needle biopsy of metastatic nodes is desirable.

4.7 Dental care to be completed (see Appendix III).

5.0 RANDOMIZATION

5.1 Patients will be stratified according to the following factors:

5.1.1 Region of primary.

5.1.2 Extent of the primary tumor. (T stages)

5.1.3 Institution.

5.2 Call RTOG Headquarters for randomization at (215) 574-3191 between 9:00 a.m. and 5:00 p.m., ET, Monday through Friday. The following information will be requested:

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 and N classifications

5.2.7 Geographic subset (if these have been indicated by the 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 should begin within 14 days after randomization.

6.0 THERAPY.

6.1 Radiation Therapy 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 Radiotherapy 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 form.

6.3 Radiotherapy 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 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 value 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

6.5.2 Primary target volume doses.

6.5.2.1 "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:

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

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 6.1 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

6.5.2.3 Photons plus surgery. Preoperative radiation will deliver a target absorbed dose of 5000 rad in 25 to 28 fractions given over 5 to 5-1/2 weeks to the primary and secondary target volume. With

postoperative radiation, an additional 1000 rad given in 5 treatments in one week may be delivered to the primary target volume.

Surgery should be performed 4 to 6 weeks following preoperative radiation therapy. Postoperative radiation therapy should begin as soon as possible, but no later than 4 weeks following surgery.

6.5.2.4 "Mixed Beam" plus surgery. Preoperative radiation will deliver a target absorbed dose to the primary target volume of

Fermilab	1600 rad
Tamvec	1550 rad
Glanta	1450 rad
Seattle	1350 rad

These doses should be delivered in 5 weeks using 3 or 4 fractions per week. The secondary target volume should be treated with 4500 to 5000 rad of photons delivered in 5 weeks using 3 or 5 fractions per week.

With postoperative radiation, the primary target volume may be given a boost of

Fermilab	350 rad
Tamvec	300 rad
Glanta	300 rad
Seattle	250 rad

delivered in 3 or 4 fractions in one week. Surgery should be performed in the same time period stated in 6.5.2.3.

6.5.3 Secondary target volume dose. 4500 to 5000 rad with photons calculated at D max 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.

6.5.4 Dose uniformity in the primary target volume. Dose gradiants 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 Maximum Dose to Critical Structures.

The spinal cord dose should not exceed 5000 rad/5 wks with photons or the equivalent with "mixed" beam based on the formula:

$$D_\gamma + 4\ D_n \leq 5000 \text{ rad.}$$

7.0 TREATMENT OF NODES.

Treatment of nodes will be at the discretion of the participating institution. The following treatments are included as preferred guidelines:

7.1 N_0 - 5000 rad or equivalent to neck alone.

7.2 N_1 - If node is absent after 5000 rad or equivalent, give boost up to 1500 - 2000 rad or equivalent, if residual N_1 - perform radical neck dissection.

7.3 N_2, A & B - Perform radical neck dissection.

7.4 N_3, B - Bilateral neck dissection.

8.0 STUDY PARAMETERS AND FOLLOW-UP

8.1

		TIME Month												
STUDY PARAMETERS	Pre-Study	3	6	9	12	15	18	21	24	30	36	42	48	54	60

dimensions and dimensions at right angles to it, if possible; otherwise by subjective assessment of percentage regression. At Day 90 to 120 from initiation of treatment, local assessment shall include, but not be limited to:

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

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

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

8.3.2 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:

8.3.2.1 No evidence of node enlargement in the neck.

8.3.2.2 Residual induration in the neck.

8.3.2.3 Nodes palpable, whether in the irradiated area or elsewhere.

8.3.3 Presence or absence of metastases by clinical evaluation or appropriate studies.

8.3.3.1 Chest X-ray, liver function tests, bone scan or survey, etc.

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

8.3.4.1 Xerostomia.

8.3.4.2 Local pain.

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

8.3.4.4 Evidence of soft-tissue necrosis.

8.3.4.5 Evidence of bone necrosis.

8.3.4.6 Skin changes in the treated area.

8.3.5 Evidence of Rehabilitation and Swallowing Function as to:

8.3.5.1 Ability to eat solid foods or soft foods and to swallow liquids normally.

8.3.5.2 Recovery of normal speech in the absence of laryngectomy.

8.3.5.3 Esophageal speech in laryngectomized patients.

8.3.6 Performance status using the Karnofsky Scale (Appendix IV).

8.3.7 A patient's death shall be reported on Form 5. Post-mortem examination of the irradiated region is highly desirable.

9.0 STATISTICAL CONSIDERATIONS

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

a) An increase to a 70% two-year local control rate (from the current estimated rate of 50%) is desirable.

b) An improvement of this magnitude should be detected with a high degree of certainty, i.e., at least 80% using a significance level of $p = 0.05$.

c) Some treatment comparisons, e.g., that using neutrons-only versus photon plus surgery, will become possible sooner than others, depending on the treatment option chosen. The calculations below will relate to this comparison.

d) The participating institutions have estimated that they will each enter approximately 12 to 15 patients per year.

Based on these assumptions, it is anticipated that the most commonly assigned treatment will, in a period of approximately 3 years, accrue the 60 to 70 patients per arm necessary to meet the objectives stated above.

As the study progresses these estimates are subject to revision.

10.0 FORMS SUBMISSION

Form	When Due
RTOG Head and Neck On-Study Form	Within 1 week of entry including treatment planning information and copies of localization films
RTOG Head and Neck Radiotherapy Form	At completion of therapy
RTOG Head and Neck Follow-Up Form	At 3 months after randomization, then at 3 montly intervals up to 2 years, then at 6 monthly intervals
RTOG Head and Neck Operative Report	Following any therapeutic surgery

REFERENCES

1. Bewley, D.K.: Physical aspects of the fast-neutron beam. Brit J Radiol 36:81-88, 1963.

2. Catterall, M., Sutherland, I. and Bewley, D.K.: 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. Brit Med J 2:653-656, 1975.

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
- TI 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

REGION	SITE

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

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

Supraglottic Larynx

- 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 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.

Glottis:

TIS Carcinoma in situ

T1 Tumor confined to vocal cord(s) with normal mobility (includes involvement of anterior or posterior commissures).

T2 Supraglottic and/or subglottic extension of tumor with normal or impaired cord mobility.

T3 Tumor confined to the larynx with cord fixation.

T4 Massive tumor with thyroid cartilage destruction and/or extension beyond the confines of the larynx.

Nodal Involvement (N)

NX Nodes cannot be assessed

N0 No clinically positive nodes

N1 Single clinically positive homolateral node less than 3 cm in diameter

N2 Single clinically positive homolateral node 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
- 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

TNM STAGING OF CARCINOMA OF THE UPPER AIR PASSAGES, CONSTRUCTED BY THE AMERICAN JOINT COMMITTEE FOR CANCER STAGING AND END RESULTS REPORTING (1976)

Only tumors originating in the following 4 regions and 17 sites will be included:

Region 1. Oral Cavity

- Site 1. Oral Tongue (anterior to circumvallate papillae)
- Site 2. Floor of the Mouth
- Site 3. Buccal Mucosa
- Site 4. Lower gingiva (Alveolar Ridge)
- Site 5. Retromolar Gingiva

Oral Cavity

- 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 deep invasion to involve antrum, pterygoid muscles, root of tongue, or skin of neck

Region 2. Oropharynx

- Site 1. Faucial arch including soft palate and posterior tonsillar pillar
- Site 2. Tonsillar fossa and tonsil
- Site 3. Base of tongue including glossoepiglottic and pharyngoepiglottic folds
- Site 4. Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

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

Region 3. Hypopharynx

Site 1. Pyriform sinus

Site 2. Postcricoid area

Site 3. Posterior pharyngeal wall

Hypopharynx

TIS: Carcinoma in situ

T1: Tumor confined to site of origin

T2: Extension of tumor to adjacent site or region without fixation of hemilarynx

T3: Extension of tumor to adjacent site or region with fixation of hemilarynx

T4: Massive tumor invading bone or soft tissues of neck

Supraglottis

TIS: Carcinoma in situ

T1: Tumor confined to site 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 preepiglottic space

T4: Massive tumor extending beyond larynx to involve oropharynx, soft tissues of neck, or destruction of thyroid cartilage

Cervical Node Classification. Midline nodes are considered as homolateral nodes.

N0: No clinically positive node

N1: Single clinically positive homolateral node less than 3 cm in diameter

N2: Single clinically positive homolateral node 3 cm to 6 cm in diameter or multiple clinically positive homolateral nodes, none over 6 cm in diameter

N2a: Single clinically positive homolateral node 3 cm to 6 cm in diameter

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), one 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

APPENDIX III

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.

APPENDIX IV

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS[1]

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 whose 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 whose 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

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 with the use of 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 begun 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 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 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.