RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-08

EFFICACY OF A SUPPLEMENTARY NEUTRON BOOST FOLLOWING IRRADIATION OF SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY, PHARYNX AND LARYNX

Closed

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PROTOCOL FOR SUPPLEMENTAL NEUTRON THERAPY IN CARCINOMA OF THE HEAD AND NECK REGION TREATED WITH RADIATION THERAPY ONLY

SCHEMA

Stratify:

Region

- Oral Cavity/Oropharynx
- Hypopharynx/Supraglottic Larynx

Extent of Primary

- T-2, T-3, T-4

Institution

RANDOMIZE

- A. Photons 4500-5000 rad large volume plus 2500-3000 rad boost (total 7500)
- B. Photons 4500 rad large volume plus neutron boost of 830-1000 rad (equivalent to 2500-3000 rad photons)

1. Reduced fields at 4500-5000 rad wherever possible.
2. Photons 180-225 rad/fraction.

Randomization can be done any time before the boost is to be started.

Facilities may decide not to include specific regions, sites, or T and N classifications within sites.

1.0 INTRODUCTION

1.1 Rationale for Combined Neutron and 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 might result in significant subcutaneous fibrosis with some risk of major complications.

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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.

Any radiobiological advantage of fast neutron beams might be masked by the poor dose distribution. This protocol therefore uses a sequence of high energy photons followed by neutrons in one arm in an attempt to exploit the advantages of both modalities, and hopefully improve the local control rate while decreasing the potential for complications.

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 passage 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 local control rates were higher with neutrons.

Statistically these advantages to the neutron treated patients were highly significant. Radiobiological experiments also support the fact that mixtures of photons and neutrons are likely to be as effective as neutrons alone. 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.

This protocol is designed to randomly allocate patients referred only for radiation therapy to one of two treatment arms. These are: 1) treatment with standard photon radiation therapy only, and 2) photon radiation therapy plus a boost of neutron radiation to the original sites of gross disease.

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 completion 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 non-successes, insofar as the treatment with radiation therapy is concerned, if the resected specimen shows residual tumor cells. However, the results of this policy will be evaluated as it may well prove to be one of the more successful approaches in management, even of persistent (histologically positive) cases.

2.0 OBJECTIVES

In patients with T_2, T_3, or T_4 squamous carcinoma of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx:

2.1 To determine the effect of a neutron boost to the primary and palpable neck nodes following conventional radiotherapy on local tumor control compared to a boost using conventional radiotherapy;

2.2 To determine the side effects and complications of neutron boost compared to conventional radiotherapy;

2.3 To determine the incidence of distant metastases for each treatment;

2.4 To determine survival for each treatment;

2.5 To assess the quality of survival.

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:

	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 (see Appendix I).

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 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 for skin cancer.

3.2.5 General Medical Reasons. Poor general condition indicated by a Karnofsky performance status equal to or less than 50 (e.g., severe malnutrition, below 60% standard weight or factors not itemized below, which in the investigator's opinion precludes any curative effort.)

3.2.6 Exclusions. 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 enforced throughout the study.

3.2.7 Patients receiving their treatment at RTOG full member institutions or the institution of the principal investigator of the neutron facility are excluded from the protocol unless this exclusion is waived by the RTOG Group Chairman or his designee since RTOG protocol 76-10 is first priority for these patients.

4.0 STAGING AND 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 Operations Headquarters.

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 and N classification (see Appendix I).

4.4 Laboratory Studies.

4.4.1 Hemoglobin or hematocrit, WBC, differential and platelets.

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

4.5 Dental care to be completed (Appendix III).

5.0 RANDOMIZATION

May be done after photon treatment has been started.

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 Operations Headquarters for randomization (215-574-3191), between 9:00 AM and 5:00 PM, ET, Monday-Friday. The following will be required:

5.2.1 Principal Investigator's name;

5.2.2 Protocol;

5.2.3 Institution referring patient;

5.2.4 Neutron facility;

5.2.5 Patient's Name;

5.2.6 Region of tumor (oral cavity, oropharynx, hypopharynx or supraglottic larynx);

5.2.7 T classification;

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

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

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 beam in the reduced (boosted) volume lies anterior to the spinal cord. 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.

All fields will be treated daily.

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 it 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 Dose.

6.5.2.1 Initial Photon Treatment to Primary and Secondary Target Volume. A target absorbed dose including the primary and secondary target volumes of 4500-5000 rad will be delivered in 23-28 fractions in 4-1/2 - 5-1/2 weeks treating five fractions per week. Daily fractions of 180-225 rad will be used.

6.5.2.2 Photon Boost. Boosted volume: Treatment fields should be reduced to include only the primary target volume. The target absorbed doses will be 2500-3000 rad from external radiation in 2-1/2 - 4 weeks treating 5 days per week; or 3000 rad in 3 days from an interstitial implant expressed at the periphery of the boosted volume or as the minimum isodose which encompasses the tumor volume; or 2500-3000 rad in 2-1/2 - 4 weeks using electrons.

6.5.2.3 Neutron boost. Boosted volume: As in 6.5.2.2, the neutron boost will be given in 4-6 fractions in 2-3 weeks. 830 rad (2500 equivalent) to 1000 rad (3000 rad equivalent) will be given. Doses are target absorbed doses in all instances. Acceptable schedules are:

250 rad x 4 once or twice weekly
200 rad x 5 twice weekly
167 rad x 6 three times weekly

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6.5.3 Dose Uniformity in the Primary Target Volume. Dose gradiants within the target volume may range from 7-1/2% below to 7-1/2% above the target absorbed dose. Whenever possible, the dose in the primary target volume should be kept within 5% of the prescribed target absorbed dose.

6.5.4 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.

6.5.5 Maximum Dose to Critical Structures. The spinal cord dose should not exceed 5000 rad/5 weeks with photons. The boosted volume must exclude the spinal cord.

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
CBC, Platelets	x														
Photograph of treated area			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.

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 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 Primary Tumor Response. The rate of regression of the primary tumor under radiotherapy 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. 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.

7.3.2.3 Residual node enlargement in the neck.

7.3.3 Presence or Absence of Metastases by Clinical Evaluation or Appropriate Studies.

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,

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.

7.3.5 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 or 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 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 treatment comparison will be between photon boost and neutron boost after standard photon treatment to 5000 rad.

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 a 55% 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.

d) That the three participating institutions will contribute approximately 15 to 20 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.

9.0 FORMS SUBMISSION

Forms are due according to the following schedule:

Form	Due
Treatment Plan Localization Films On-Study Form	Within 1 week of randomization
Localization Film of Boost	Prior to boost
Radiotherapy Form Treatment Sheets	At completion of radiotherapy
Follow-Up Form	Every 3 months for 2 years; every 6 months thereafter
Death Form	At death

REFERENCES

1. British Medical Journal, June 25, 1977.

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
- TO 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
Nasopharynx	- Posterior superior wall (vault)
	- Lateral wall
Oropharynx	- Faucial arch including soft palate, uvula, and anterior tonsillar pillar
	- Tonsillar fossa and tonsil
	- Base of tongue including glossoepiglottic and pharyngo-epiglottic 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

TO No evidence of primary tumor

Nasopharynx:

TIS Carcinoma in situ

T1 Tumor confined to one site of nasopharynx or no tumor visible (positive biopsy only)

T2 Tumor involving two sites (both posterosuperior and lateral walls)

T3 Extension of tumor into nasal cavity or oropharynx

T4 Tumor invasion of skull or cranial nerve involvement, or both

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

Larynx: Primary Tumor (T)

TX Tumor that cannot be assessed by rules as listed in 2.0

T0 No evidence of primary tumor

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_____

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

STAGE GROUPING

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

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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.

APPENDIX III

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 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

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 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.