RADIATION THERAPY GROUP

PROTOCOL TO STUDY NEUTRON THERAPY IN THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY USING RADIATION THERAPY FOLLOWING CHEMOTHERAPY AS THE ONLY PLANNED TREATMENT MODALITY.

SCHEMA

Stage III and IV Inoperable Oral Cavity Oropharynx Hypopharynx Larynx	Chemotherapy 2-3 Cycles	Standard Radiation Therapy 6600-7400 rads 6-8 weeks. Neutron Radiation Therapy 1900-2200 rads 4 weeks, 9 fractions.

1 INTRODUCTION

2 The use of chemotherapy prior to radiation therapy and or surgery is becoming increasingly popular for patients with advanced mouth and throat cancers. For patients not suitable for a definitive operation the questions of the optimal type of radiation (neutrons versus photons) and the optimal dose (tumor control versus complications) has not been settled. Most current studies addressing these questions preclude prior chemotherapy. In an effort to obtain more clinical information bearing on optimal dose and type of radiation, a study is proposed to permit entry of patients with a planned two or three cycles of pre-radiation chemotherapy. This permits assessment of chemotherapy response rates and may favorably influence the response of local disease to the radiation and/or improve survival from control of occult distant metastases.

2.1 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 patients 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 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 a failure of host resistance and general dissemination. Controlled randomized trials in Europe have shown only an 8-10% improvement of neutron treatment over photon treatment. The Fermilab experience has been consistant with these studies (Stage II N 3/3 P 7/11, Stage III N 2/4 P 9/23, Stage IV N 8/19 P 16/45). There is clearly a 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, and combinations of any of these with salvage 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.

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 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.

2.2 OBJECTIVES

2.3 Assessment will be made of primary endpoints.

2.3.1 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:

2.3.1.1 Clinical absence of local disease.

2.3.1.2 Biopsy-proven evidence of recurrence.

2.3.2 Length of survival and tumor and functional status at time of death.

2.3.3 Complications due to diverse forms of therapy.

2.3.4 Assessment of rehabilitation and functional status post therapy. The Karnofsky scale will be used (See Appendix I).

3 PATIENT SELECTION

3.1 Eligibility.

3.1.1 Sites (see Appendix II).

3.1.1.1 Oral Cavity - Stage III, IV.

3.1.1.2 Oropharynx - Stage III, IV (Base of Tongue - Stage II also).

3.1.1.3 Hypopharynx - Stage III, IV.

3.1.1.4 Larynx (including supraglottis) - Stage III, IV.

3.1.2 Biopsy proven carcinoma.

3.1.3 No previous radiation therapy.

3.1.4 No evidence of distant metastatic disease.

3.1.5 No plan for resection of primary following irradiation.

3.1.6 Age > 18 but there will be no upper age limit as long as general medical requirements (3.2.6) are met.

3.1.7 Performance Status (Karnofsky) $\geq$50.

3.2 Ineligibility Criteria.

Patients are eliminated from the study for the following reasons:

3.2.1 Tumor is classified Stage I or II, except base of tongue primaries where Stage II is eligible.

3.2.2 Patients with distant metastases.

3.2.3 Patients with two simultaneous tumors, regardless of location of second primary.

3.2.4 Previous radiation therapy of the head and neck, except for skin cancer.

3.2.5 Prior surgery (except diagnostic) to primary site or nodes.

3.2.6 General medical reasons:

3.2.6.1 Poor general condition indicated by a Karnofsky performance status less than 50 (eg., severe malnutrition, below 60% standard weight) or conditions which in the investigator's opinion precludes any curative effort.

4 PRETREATMENT EVALUATION.

4.1 Complete history and physical examination with an assessment of the patient's performance status. Diagrams of the primary and any nodal metastases must be made.

4.2 Imaging Studies

4.2.1 Required

4.2.1.1 Chest x-ray

4.2.1.2 Liver scan if liver enzymes are elevated

4.2.1.3 Other pertinent radiographs depending on location of primary

4.3 Satisfactory biopsy of the primary

4.4 Dental care (See Appendix III)

5 REGISTRATION

5.1 Patients should be registered prior to treatment. The following information will be required:

Principal Investigator's Name

Institution

Protocol

Patient's Name

Site and Region of Tumor

Stage

A project case number will be assigned which will be confirmed by mail.

5.2 Treatment should begin within 14 days after registration.

6 TREATMENT

6.1 Radiotherapy.

6.1.1 Localization requirements.

6.1.1.1 Simulation of treatment fields is desirable but not mandatory. The field borders must initially include the entire primary region (e.g., tongue/oropharynx) and bilateral cervical nodes. For all pyriform sinus (hypopharyngeal) primaries and for all T4 tonsillar lesions, the superior field must extend to the base of the skull. The superior, posterior field border must at least encompass the mastoid tip. The entire neck must be treated to the superior edge of the clavicles. Separate anterior supraclavicular fields should be used.

6.1.1.2 Portal films should be repeated every two weeks during therapy and whenever any field adjustments are carried out.

6.1.1.3 Verification ("beam") films must be obtained on each treatment portal irradiated including all cone-down or boost fields.

6.2 Target Volume

6.2.1 Dose calculations

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

curves are desirable but not required.

6.2.1.2 Variation within the target volume should not exceed ±7.5% of the target dose.

6.2.1.3 Fields must encompass the primary tumor and its suspected projections with a minimum 1.5 cm margin in all directions. This tumor (target) volume should receive 90% or greater of the central axis mid-depth dose. Fields may be reduced in dimensions if tumor regression occurs after 75% of the total dose. Fields must be reduced to exclude the spinal cord at a dose of 1200 cGy neutrons or 4500 cGy photons at midline.

6.2.2 Fractionation

6.2.2.1 Neutron fractionation will be 2 fractions per week, giving equal daily doses. A total of 9 fractions will be given in 4 weeks.

6.2.3 Doses

The following target absorbed doses will be delivered in 9 fractions using 2 fractions per week (over 26 days). A total target absorbed dose of 1900-2200 Fermilab neutron rads.

6.2.3.1 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 to the principal target volume. Daily fractionation (5 per week) of 180 to 200 rad will be used at all times. In selected appropriate cases, the boost to the principal target volume may be done by interstitial implantation of radioactive sources.

6.2.4 Secondary Target Volume Dose. 4500 to 5000 rad with photons or the equivalent with neutrons (ranging from 1500-1600 rad at Fermilab to 1250-1350 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.

6.2.5 Dose Uniformity in the Primary Target Volume. Dose gradients within the primary target volume may range from 7.5% below to 7.5% above the target absorbed dose. Whenever possible, the dose in the target volume should be kept within 5% of the prescribed target absorbed dose.

6.2.6 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.

7 DRUG THERAPY

Pre-radiation chemotherapy may be up to three cycles of any of the adjuvant chemotherapy protocols. The radiation therapy should be started as soon as the acute mucosal and hematologic reactions have recovered. This will usually be 2-4 weeks.

8 SURGERY

8.1 Primary. Surgical removal of the primary should not be planned unless persistent cancer is proven by biopsy 6 weeks or more following completion of radiotherapy. Under these circumstances, the patient will be considered as a treatment failure. Patients who are originally operable (suitable for a combined-treatment approach) are ineligible for this study.

8.2 Regional Nodes. Partial or radical neck dissections may be performed for persistent lymph nodes at the completion of radiotherapy or as planned procedure for nodes originally measuring > 3 cm in diameter.

9 OTHER THERAPY

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

10 PATHOLOGY

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

Grade I - well differentiated or Keratinizing Grade II - moderately differentiated or Typical Grade III - poorly differentiated or anaplastic "Lymphoepithelioma" will be considered a variant within the Grade III category.

Central pathology review is not planned.

11 PATIENT ASSESSMENTS

11.1 Endpoints of the study will include:

11.1.1 Completeness of tumor regression

11.1.2 Acute toxicity of radiotherapy

11.1.3 Local control

11.2 Measurements of Specific Endpoints

Response shall be measured as follows:

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

11.2.1.1 Complete response (CR) - Complete disappearance of measurable and palpable tumor.

11.2.1.2 Partial response (PR) - Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions.

11.2.1.3 Minor response (MR) - Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions.

11.2.1.4 No change (NC) - 25% growth to 25% shrinkage of the product of the perpendicular diameters of the two largest dimensions.

11.2.1.5 Progressive disease (PD) - Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions.

11.2.2 Status of Neck - Weekly measurements should be made during treatment if any measurable neck nodes are present. An assessment should be made including:
No evidence of node enlargement in the neck.
Residual induration in the neck.

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

11.2.4 Toxicity of radiotherapy
Weekly assessments of mucositis and skin reactions will be made during radiotherapy and following treatment until all such reactions subside. The RTOG acute scoring scale will be used.

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

11.3 Study Parameters.

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

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

++ Clinical examination and x-rays for tumor measurements will be performed 4 weeks after treatment then q 2 months the first and second year, q 3 months the third year and q 4 months thereafter.

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

a. Primary tumor site.

b. Regional nodes.

c. Metastatic visceral spread.

d. Treatment complications.

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

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

12 DATA COLLECTION

Data are due according to the following schedule:

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

13 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 neutron 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 $p = 0.05$.

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 - 2.5 years of patient accession in order to accumulate the 70 to 80 patients per arm required to meet the above objective.

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

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

REFERENCES

1. Catterall, M., Sutherland, I., 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. Br. J. Med. 2:653-656, 1975.

APPENDIX I

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.

APPENDIX II

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

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

N0 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.

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 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 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

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 hepatitic 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	