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RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-28

PI MESON RADIOTHERAPY* OF CARCINOMA OF THE ORAL CAVITY (EXCLUDING LIP) AND PHARYNX

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SCHEMA

Stratify

Region
- Oral Cavity
- Oropharynx
- Nasopharynx
- Hypopharynx

Stage
- Stage III (T3, N1)
- Stage IV (T4, any N or any T, N2 or N3)

RANDOMIZE

- Conventional treatment
  - Photons[a] only
  - Photons[b] combined with surgery
- Pion Radiotherapy[c]

a. 6600 rad/6-1/2 to 7-1/2 wk to 7500 rad/7-1/2 to 9 wk.

b. 5000 rad 5-6 wk preoperative (except nasopharynx).

c. Minimum of 3600 peak pion rad at a minimum of 100 peak pion rad/day, calculated at the 80% isodose line. (The minimum dose is approximately 2 cm peripheral to the 95% isodose line.) Maximum of 4500 peak pion rad at 125 rad/day at 100% isodose line. Cone-down boost to a total of 3840 peak pion rad minimum and 4800 peak pion rad maximum may be added for persistent disease.

1.0 INTRODUCTION

1.1 Definition of the Problem.

Patients presenting with mucosal (squamous) carcinomas of the head and neck region form a therapeutic challenge. These patients frequently present with advanced tumors in an inoperable state due to extensive primaries or advanced lymph node metastases, or both. Several studies have reported overall survival rates varying from 7 to 45% in Stage III and IV (T3 and T4) carcinomas of the oral cavity and oropharynx. In patients presenting with clinically palpable cervical lymph nodes, the five-year survival is approximately one-third that of patients without palpable nodes, even when adjusted for T-Stage.

Treatment failure for oral cavity cancer is frequent in higher stages of the disease. However, failures are generally due to locally and regionally recurrent cancer. This site, therefore, is a favorable one for evaluating the possible beneficial effects of pion radiation therapy. Table I emphasizes the relationship of failure rate to stage, as derived from data presented by Chu and Fletcher in 1973 (1). Strictly comparable data for lesions of the lower gingivae and buccal mucosa are not available. However, the data (2) of Table 2 are indicative of the problem of local control in these sites.

Five-year survival data (3) collected in an AJC field trial of 1,570 patient records (Table 3) illustrate a marked difference in prognosis for cases categorized as Stage III and IV, compared with Stage I and II (according to 1968 staging criteria).

Table 1. Failure to Control Primary Lesion (January 1948 - December 1968)

Site	Stage*	Number of Failures / Number of Patients	External Irradiation Only	Interstitial Irradiation Only	Combined External & Interstitial Irradiation	Patients Salvaged by Surgery (2 years)	Ultimate Failure
Anterior	T1	3/52 (5.7%)	---	3/48 (6%)	0/4 (0%)	1/33 (3%)	5.5%
2/3 Tongue	T2	17/100 (17%)	4/9 (44%)	9/55 (16%)	4/36 (11%)	5/17 (29%)	12.0%
	T3	26/66 (41%)	10/17 (59%)	3/10 (30%)	14/39 (36%)	6/27 (22%)	32.0%
	T4	20/30 (67%)	10/15 (67%)	4/6 (67%)	6/9 (67%)	2/20 (10%)	60.0%
Floor of	T1	1/49 (2%)	0/10 (0%)	1/31 (3%)	0/8 (0%)	1/1 (100%)	0/0%
Mouth	T2	9/77 (11.5%)	5/23 (22%)	3/34 (9%)	1/20 (5%)	4/9 (44%)	6.5%
	T3	14/60 (23%)	9/25 (36%)	3/17 (18%)	2/18 (11%)	11/14 (79%)	5.0%
	T4	19/24 (79%)	13/16 (81%)	2/4 (50%)	4/4 (100%)	0/19 (0%)	79%

*CRTS Staging:
T1 < 2 centimeters diameter
T2 2-4 centimeters (no invasion surrounding structures)
T3 > 4 centimeters and/or invading surrounding structures
T4 Massive tumor or bone involvement

Source: Chu and Fletcher (1)

Table 2. Failure to Control Primary Lesions of Buccal Mucosa and Lower Gum with Radical Radiation (3YR F/U)

Site	Number of Patients	Stage* T1	T2	T3	
Lower Gingiva	14	0/4	0/5	3/5	No Surgical Salvage
Buccal Mucosa	21	0/7	0/5	0/9	

*CRTS Staging: T1 < 3 centimeters diameter

T2 3-5 centimeters (minimal extent to adjacent structures)

T3 > 5 centimeters

T4 Massive invasion or bone infiltration

Source: Fletcher, MacComb, and Braun (2)

Table 3. Five-Year Survival, by Stage, of 1570 Patients with Carcinoma of the Oral Cavity

	Buccal Mucosa			
	N0	N1	N2	N3
T1 Stage 1	72%	5/8	---	---
T2 Stage 2	61%	9/25	---	---
T3	8/15*	5/17	0/3	0/8
Stage 3 = 42%			Stage 4 = 0%	

	Floor of Mouth			
	N0	N1	N2	N3
T2 Stage 1	21/31 68%	2/2	0/1	0/5
T2 Stage 2	21/29 70%	12/23	1/5	2/8
T3	4/9	5/12	0/4	0/10
Stage 3 = 50%			Stage 4 = 9%	

	Anterior 2/3 Tongue			
	N0	N1	N2	N3
T1 Stage 1	90%	1/4	---	---
T2 Stage 2	64%	6/21	0/1	0/3
T3	8/15	1/7	0/6	1/17
Stage 3 = 34%			Stage 4 = 6%	

	Posterior 1/3 Tongue			
	N0	N1	N2	N3
T1 Stage 1		4/8	0/5	0/4
T2 Stage 2	15/34 44%	7/15	3/13	1/10
T3	2/15	4/26	0/8	2/21
Stage 3 = 26%			Stage 4 = 7%	

*Number of patients living five years
Total number of patients in group

Source: AJC 1968 (3)

Table 3 (continued)

Soft Palate

	NO	N1	N2	N3
T1 Stage 1	73%	2/6	0/2	1/1
T2 Stage 2	48%	5/8	0/2	0/2
T3	9/27*	0/9	0/4	0/9
Stage 3 = 32%				

Hard Palate

	NO	N1	N2	N3
T1 Stage 1	14/15 93%	--	--	--
T2 Stage 2	10/25 40%	1/3	--	0/4
T3	4/22	1/12	1/3	0/5
Stage 3 = 16%			Stage 4 = 8%	

Lower Alveolar Ridge

	NO	N1	N2	N3
T1 Stage 1	64%	5/7	0/1	0/3
T2 Stage 2	49%	6/12	--	2/7
T3	2/18	8/18	0/6	1/13
Stage 3 = 37%			Stage 4 = 10%	

Upper Alveolar Ridge

	NO	N1	N2	N3
T1 Stage 1	8/13	1/3	--	--
T2 Stage 2	18/28 64%	3/6	--	--
T3	9/24	2/9	--	1/4
Stage 3 = 36%			Stage 4 = 1/4	

*Number of patients living five years

Total number of patients in group

Source: AJC 1968 (3)

Similar data and comments are appropriate in the consideration of advanced (T3-T4) cancer sites within the oropharynx. Table 4 summarizes data from several RTOG studies relevant to stage, local control, and median survival.

Table 4. Reported Parameters for RTOG Head and Neck Studies

Site	% with T3 & T4 Lesions	% with Clinically Positive Nodes	Control at 1 yr.(%)	Median Survival (mos.)
Oropharynx	70-85	68-80	65 (T3)	18
			33 (T4)	10
Tonsillar Fossa	88	75	59 (T3)	26
			37 (T4)	6
Base of Tongue	89	74	45 (T3)	16
			18 (T4)	11

Advanced carcinomas of the nasopharynx (bone destruction, cranial nerve involvement) have unacceptably high failure rates with only a few patients, in most series, reported with control of primary (4, 5).

Carcinomas involving the hypopharynx may spread to involve other structures, such as the larynx (particularly through the laryngeal ventricle, infiltrating the true and false vocal cords), the lateral wing of the thyroid cartilage, or the internal carotid artery, or may produce an external tumefaction.

Lymphatic metastases, which are very frequent, are routed through channels existing from the thyrohyoid membrane to the jugulodiagastric, jugulocarotid, or jugulo-omohyoid nodes.

The incidence of clinically recognized distant blood-borne metastases would be much higher if local control was better and long-term survival more frequent. About one-half of those patients enjoying local tumor control eventually (within three to seven years) suffer distant metastases.

Local control of tumor and consequent long-term, tumor-free survival vary with tumor extent. Inasmuch as more than two-thirds of these patients have Stage III or IV disease at the time of diagnosis (6), the overall tumor-free survival is low - 15 to 30 percent (6,7).

1.2 Rationale for Pion Radiotherapy.

The rationale for pion radiotherapy is primarily related to two factors: (1) a different biological response in the stopping region of the pion beam from that seen in conventional radiation, and (2) the capability for localizing this differential response within the target volume, largely sparing normal surrounding tissue.

With high-linear-energy-transfer (high-LET) radiation (for example, neutrons, pions, and heavy ions), there is increased irreparable damage of critical molecules (i.e., double-strand breaks in DNA), as compared to the type of damage caused by low-LET radiation (e.g., x-rays, gamma rays of cobalt, electrons, and protons). In addition, cells exposed to low-LET radiation exhibit up to three times more resistance to injury if they are not well oxygenated. Thus, hypoxic cells, large numbers of which are usually present in tumors, are less sensitive to damage than are well oxygenated cells of the tumor and the surrounding normal tissue. The dense ionization of high-LET radiation may overcome the protective effect of hypoxia, killing those cells almost as effectively as well-oxygenated cells. Further, cells are more resistant to low-LET radiation in certain phases of the cell cycle than in others. High-LET radiation reduces differences in cellular sensitivity due to cell cycle variations.

Heavy charged particles, such as pions and heavy ions, distribute their dose with a Bragg peak, a region of intense radiation which can be located in the tumor volume.

Pions have the advantages of both high-LET and low-LET radiation, because they deposit low-LET radiation as they pass through tissue (plateau region), but produce a high-LET component in the stopping (tumor) region. Due to their negative charge, the stopping pions are absorbed by the positively charged nuclei of oxygen, carbon, and nitrogen atoms. This excess energy makes the nuclei unstable and they disintegrate, producing neutrons, protons, deuterons, tritons, alpha particles, and heavy ions. These events increase the total dose in the pion stopping region and alter the biological effectiveness of the dose in that region because of the dense ionization produced mainly by the alpha particles, heavy ions and neutrons.

Results to date of Phase I-II studies of pion radiotherapy, being conducted at the Los Alamos Meson Physics Facility (LAMPF), by the University of New Mexico Cancer Research and Treatment Center, suggest therapeutic advantages in the treatment of many advanced solid tumors with pion radiotherapy. Patients with primary and metastatic tumors of the skin, head and neck, lung, abdomen and pelvis have been irradiated with pions to assess tolerance of normal tissues and tumor response. Early studies with metastatic tumor nodules in the skin established a relative biological effectiveness (RBE) of 1.42 for pions, as compared to 100 kVP x-rays, for acute skin injury (8). Subsequently, analysis of time to regrowth of 16 nodules (primary breast) in one patient participating in that study who could be followed for 346 days suggested the possibility of therapeutic gain of 37% for pions versus x-rays (9).

A report on 40 patients treated for large deep-seated lesions, all of whom were followed for 6 to 15 months, showed that pion radiotherapy was well tolerated at doses ranging from 1000 to

4600 peak pion rad, delivered generally in five fractions per week with daily fraction sizes of 110 to 140 peak pion rad maximum. Complete regressions occurred in approximately half those patients treated with pions alone at maximum doses of more than 2700 peak pion rad. No complete regressions occurred in patients treated with pions alone at doses under 2700 peak pion rad. Conventional radiation and/or surgery was well tolerated by those patients requiring those treatments after pion radiotherapy. Reactions in the normal tissues within the plateau and the peak regions have been similar to those which would be expected with conventional radiation delivered to acute tolerance. Severe late reactions have included one patient with chronic, severe laryngeal edema following 5000 peak pion rad given in 7 weeks for a T4 carcinoma of the larynx. The patient expired of lung metastases 14 months after therapy with no evidence of local disease. A patient with a T3, N2A, M0 carcinoma of the tonsil developed severe soft tissue and mandibular necrosis 5 months after 4600 peak pion rad in 6 weeks necessitating extensive surgical reconstruction.

It is estimated that some 60,000 perons die in the United States each year because of lack of tumor control at the primary site. Pions are being tested on those types of large tumors which are not well managed by any other treatment or combination of treatments, to attempt to improve the survival in this group of patients. In addition, any large reduction in the body's total burden of tumor cells may improve the chances for cure by conventional techniques (surgery, radiotherapy, and chemotherapy, alone or in combination). Thus, potentially additional patients can be helped by pion radiotherapy if their large tumor masses can be eliminated or significantly reduced.

Considering the modest 1-year tumor control rates for Stage III and IV cancers of the oral cavity and pharynx, controlled clinical trials using pi mesons seem warranted.

2.0 OBJECTIVES

In patients with Stage III or IV (T3 and T4) squamous cell carcinoma of the oral cavity and pharynx:

2.1 To determine if local tumor control of the primary is improved using pion radiotherapy compared to conventional treatment.

2.2 To determine the incidence of distant metastases as related to the various forms of treatment.

2.3 To determine if patient survival is improved using pion radiotherapy compared to conventional treatment.

2.4 To determine the morbidity of radiotherapy.

2.5 To assess the complications of therapy.

2.6 To assess the quality of survival related to the various forms of treatment.

3.0 PATIENT SELECTION (ELIGIBILITY)

3.1 Eligibility Criteria.

3.1.1 Previously untreated, Stage III (T3, N1) or IV (T4, any N or any T, N1 or N2) (AJC-see Appendix I) squamous cell carcinoma of the oral cavity (except lip) or oropharynx, nasopharynx or hypopharynx.

3.1.2 Biopsy proven squamous cell carcinoma.

3.1.3 Patients with tumors originating in the following regions and sites:

Region	Site
Oral Cavity	Oral Tongue
	Floor of Mouth
	Buccal Mucosa
	Lower Gingiva
	Upper Gingiva
	Retromolar Gingiva
	Hard Palate

Oropharynx	Faucial Arch
	Tonsillar Fossa and Tonsil
	Base of Tongue
	(Glossoepiglottic and
	Pharyngoepiglottic folds)
	Pharyngeal Wall
	(Lateral and Posterior Wall,
	Posterior Tonsillar Pillar)
Nasopharynx	Posterior Superior Wall (Vault)
	Lateral Wall
Hypopharynx	Pyriform Sinus
	Postcricord Area
	Posterior Hypopharyngeal Wall

3.1.4 Tumor must be AJC Stage III (T3, N1) or IV (T4, any N or any T, N2 or N3).

3.1.5 Karnofsky performance status $\geq$ 60 (See Appendix II). Able to travel to and be treated at Los Alamos if randomized to pion radiotherapy.

3.1.6 Patients with previous malignancies who have been disease free for more than eight years or for at least three years for primary skin cancer (excluding melanoma and carcinoma of the lip).

3.1.7 Agreement of the patient's physician to the conditions of the protocol (including diagnostic studies and treatment randomizations) and to relinquish management of the patient's treatment to the study team.

3.1.8 Completion of the required investigational consent form.

3.1.9 Patient must not be < 18 or > 75 years of age.

3.2 Ineligibility Criteria.

3.2.1 AJC Stage I or II carcinoma (see Appendix I).

3.2.2 Carcinoma of the lip.

3.2.3 Verrucous carcinoma or histology other than squamous cell carcinoma.

3.2.4 Evidence of distant metastases (beyond the cervical lymph nodes).

3.2.5 Previous definitive therapy of the primary tumor and regional adenopathy, including prior definitive radiation therapy or potentially curative surgical procedures. Excision of a tumor-bearing node is not considered therapy.

3.2.6 Previous chemotherapy, which, in the opinion of the study team, might compromise treatment or evaluation.

3.2.7 Previous radiotherapy to areas overlapping the projected treatment portals.

3.2.8 Active, uncontrollable infection in the area of contemplated irradiation.

3.2.9 Medical, psychological or other contraindication to the contemplated diagnostic or therapeutic measures and their evaluation, or to long term follow-up.

3.2.10 Evidence of a second malignancy, other than skin cancer. (For patients with second malignancies other than skin cancer, the disease-free interval must exceed eight years. For patients with skin cancer, the disease must have been under control for at least three years. Skin cancer, for the purposes of this study, does not include melanoma or cancer of the lip.)

4.0 PRETREATMENT EVALUATION

Consistent with good medical practice, the following will be performed on initial evaluation prior to admitting the patient to the study. Results of the evaluation will be used to determine patient eligibility for the study and in management of his treatment regimen.

4.1 Medical History.

4.1.1 Age.

4.1.2 Sex.

4.1.3 Race.

4.1.4 Date of onset of symptoms (month and year in which the patient first noticed definite symptoms or signs which are later explained by the disease).

4.1.5 Date (month and year) of definite diagnosis of disease.

4.1.6 Description of symptoms.

4.1.7 Other illnesses.

4.1.8 Medications currently used.

4.1.9 Previous therapy (if any).

4.2 Physical Examination.

4.2.1 Height.

4.2.2 Weight.

4.2.3 Temperature.

4.2.4 Performance Status (Karnofsky function assessment).

4.2.5 Drawing of primary tumor and regional adenopathy (with centimeter dimensions); also, photographs, if possible.

4.3 Routine Laboratory Tests.

4.3.1 Complete blood count including white count, differential and platelets.

4.3.2 Urinalysis.

4.3.3 Blood chemistries including serum alkaline phosphatase, SGOT, total protein, and albumin.

4.3.4 Immune reactivity tests, when possible (optional).

4.3.5 Others, as indicated by the individual patient's condition.

4.4 Routine Imaging Procedures.

4.4.1 Chest x-ray (posterior-anterior and lateral).

4.4.2 Others, as indicated (e.g., bone scan or x-rays of mandible and maxilla, if bone involvement is suspected).

4.4.3 CT scans if available; if not, this will be performed at the Study Center.

4.5 Optional Studies.

4.5.1 Cardiopulmonary assessment, if indicated, to tolerate 7000 feet altitude of Los Alamos.

4.5.2 Other studies as indicated, particularly to rule out distant metastasis.

4.6 Staging Procedures.

4.6.1 Biopsy of primary tumor.

4.6.2 Random biopsies of oral mucosa if field cancerization is suspected; map area.

5.0 ADMISSION TO STUDY AND RANDOMIZATION

Patients will be admitted to the study only after the pretreatment evaluation is completed and the eligibility criteria are met. Copies of all necessary forms will be forwarded to RTOG Headquarters.

5.1 All therapy will be scheduled through the Cancer Research and Treatment Center in Albuquerque. It is planned to have all patients receive radiotherapy planning CT scans and localization in Los Alamos even if randomized to conventional treatment at the referring institution. Ophthalmologic examination to assess lens opacity will be performed upon admission to the study. The following steps must be completed:

5.1.1 Identification and registration (see 5.1.2) of all patients entering the participating institution with a diagnosis of carcinoma of the oral cavity or pharynx.

5.1.2 Completion of RTOG initial registry form. (Patients who are determined by their physician as ineligible will be eliminated at this point. The RTOG initial registry form must list the reason(s) for ineligibility and be forwarded to RTOG Headquarters for use in population control).

5.1.3 Pretreatment evaluation.

5.1.4 Completion of the study entrance form (patient's name and address, referring institution, referring physician, etc.).

5.1.5 Completion of patient consent form.

5.1.6 Notification of Dr. Bush (505-277-3539) or his designee for randomization of potentially eligible patients who have agreed to participate in the study.

5.2 When a patient has been fully evaluated and determined eligible and the forms completed as specified in 5.1, Dr. Bush or his designee at the pion facility will complete and submit the on study form and will phone RTOG Headquarters at (215) 574-3191, from 9:00 a.m. - 5:00 p.m., EST, Monday through Friday, and relate the following information:

5.2.1 Protocol Name.

5.2.2 Patient Name.

5.2.3 Referring institution and physician.

5.2.4 Tumor region - oral cavity, oropharynx, nasopharynx or hypopharynx (specify exact site).

5.2.5 T and N Stage.

A project case number and treatment will be assigned by RTOG Headquarters of either:

a) Conventional therapy at the referring institution consisting of radiotherapy alone or radiotherapy combined with surgery, or

b) Pion radiotherapy at Los Alamos. These will be confirmed by mail to Dr. Bush and the referring physician.

6.0 TREATMENT DETAILS

Dental care should be completed (see Appendix III). If any teeth have been extracted, a minimum delay of two weeks from the day of extraction will elapse before beginning radiotherapy.

6.1 Conventional Radiotherapy.

6.1.1 Doses. Tumor doses will be expressed in rad calculated at the central axis of the field in the midplane between the two opposing fields, when these are employed or at the intersection of the central axis of the beams when alternate techniques are used. If a single anterior lower neck field is used, the dose will be expressed at a 3 cm depth. The minimum dose to the tumor when radiation alone is given will be 6600 rad in 6-1/2 to 7-1/2 weeks while the maximum tumor dose to the boosted volume will not exceed 7500 rad in 7-1/2 to 9 weeks. When radiation is combined with surgery the preoperative radiation dose will be 5000 rad in 5-6 weeks. The dose across the target volume should not vary more than ± 10% from these levels.

6.1.2 Fractionation. Five fractions per week of 170 to 200 rad each will be employed. The total time will be 6-1/2 to 7-1/2 weeks (7-1/2 to 9 weeks if a boost is added). 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 in 6.1.1.

6.1.3 Portals. A combination of lateral opposing fields, anterior and lateral wedged fields, or several fields will be used for the primary tumor at the discretion of the investigator in the case. Whenever possible a single anterior A-P field with a mid-line block will be used to treat the neck below the fields for the primary tumor. This lower neck field should abut the primary field at the skin. The primary tumor fields will encompass the known or suspected disease with a minimum margin of 1 cm around the tumor. At the neck level these fields will extend posteriorly at least to the level of the most posterior aspect of the mastoid prominence even in the absence of palpable nodes.

6.1.4 Technical Factors. Irradiation will be given with cobalt teletherapy or supervoltage energy equipment (4 MeV or greater). Electron beam may be used as a boost. The treatment distance will be 75 cm or more to the skin for SSD techniques or 80 cm to the isocenter for SAD techniques. The patient may be treated sitting up, lying on the side, or in the supine position. The head should be resting on a head-holder, immobilized with whatever system is available. The beam should be shaped with blocks to avoid unnecessary irradiation of normal structures like the larynx, spinal cord, etc. Whenever possible, cobalt teletherapy units should employ beam penumbra trimmers.

6.1.5 Field Reduction. After dose of 4500 to 5000 rad has been delivered, the therapist must reduce the field size by blocking parts of it or by reducing the entire field (see 6.1.6.1). After 4600 rad midplane, central dose, the spinal cord must be protected by field reduction or blocking.

6.1.6 Treatment Following 5000 Rad. After an uninterrupted dose (or interrupted as in 6.1.2) of 5000 rad has been administered, the case may be re-evaluated for continued radiotherapy or a surgical resection, except for nasopharynx primaries, which should be treated without consideration of surgery.

6.1.6.1 Continued Radiotherapy. Additional irradiation will be delivered to the primary and palpable nodes: 1500-2500 rad additional (maximum total tumor dose 7500 rad) from external radiation in 1-1/2 to 3 weeks, treating 5 days per week; or 3000 rad in 3-4 days (maximum total tumor dose 8000 rad) from an interstitial implant. The calculated dose from an implant will be expressed at the periphery of the boosted volume or as the minimum isodose which encompasses the tumor volume; or electron beam, 2000-3000 rad in 2 to 4 weeks (maximum total tumor dose 8000 rad).

6.1.6.2 Surgery - If Resectable After Preoperative Radiotherapy. The surgical procedure must be performed within 3 to 5 weeks following completion of radiation therapy. Surgery will consist of radical excision of the primary lesion with or without neck dissection. Immediate complication of surgery will be assessed.

6.1.7 Treatment of Nodes. Treatment of nodes will be according to institutional policy, except that prophylactic irradiation of clinically negative neck nodes is mandatory. The following treatments are included as preferred guidelines. Neck dissection is not recommended in patients in whom the primary is not controlled. Neck dissection, if performed, will be radical, modified radical or limited neck dissection.

N0 - 5000 rad to neck alone.

N1 - If node is absent after 5000 rad, give boost up to 1500-2000 rad, if residual N1 - perform neck dissection.

N2 A&B - Perform neck dissection if primary is controlled by radiation or if primary is resectable with radiation.

N3A - Perform neck dissection if technically feasible after radiation or if primary is resectable.

N3B - Bilateral neck dissection if primary is controlled by radiation or if primary is resectable after radiation.

Neck dissections should not be performed in cases of nasopharynx primaries, except in treatment of persistent nodes.

6.1.8 Treatment Planning. Localizing films of each field will be taken and sent to the RTOG Office in the first week of therapy together with a copy of the treatment plan. Isodose distributions will be submitted to RTOG Headquarters with the Radiotherapy Form at the completion of radiotherapy.

6.1.9 Dosimetry Monitoring. The Radiological Physics Center in Houston will conduct field surveys to verify the accuracy of dosimetry at each participating institution.

6.2 Pion Therapy.

The tumor dose will be 3600 minimum peak pion rad at the 80% isodose line, i.e., approximately 2 cm from the 95% isodose line or gross tumor margin. (The maximum dose, at the 100% isodose, will be 4500 peak pion rad.) The minimum dose prescribed is the minimum dose to the target volume, which includes the local lymphatic spread in those instances where such lymphatic spread is contiguous with or near the gross tumor volume. The minimum dose may have to be reduced if the treatment plan indicates that a critical structure (such as spinal cord) will receive a dose which exceeds its tolerance. The limit for spinal cord treated to partial thickness is 2000 peak pion rad, and for spinal cord treated to full thickness is 1750 peak pion rad. The daily minimum tumor dose will be 100 peak pion rad. Split course treatment may be needed to conform to accelerator operating schedules.

Treatment of nodes will follow the same guidelines as defined under 6.1.7 above. Involved nodes may or may not be treated with peak pions, depending on the decision of the radiation therapist as to whether the nodes may be better managed by pion radiation, conventional methods (radiation therapy, surgery, and/or implant), or a combination. Involved nodes which lie within the plateau pion field will be treated with curative intent using conventional methods (additive radiation therapy, surgery, and/or implant). (Biological studies indicate the RBE in the plateau is 1.0.) If conventional radiation is used, the type of radiation will be electrons, unless the structures are too thick, in which case supervoltage x-rays or cobalt-60 teletherapy may be used. The conventional radiation will be directed to avoid overlapping the primary pion-treated site. If, for whatever reason, the full prescribed dose of pion radiotherapy cannot be delivered, additive conventional radiation may be delivered to the primary field, to a dose level to be determined on an individual patient basis. Patients who receive such additive conventional therapy to the primary field will be retained on study, but will be stratified separately for statistical analysis.

7.0 ENDPOINTS OF STUDY AND RESPONSE CRITERIA

Primary endpoints will be derived from:

7.1 Patient survival time.

7.2 Quality of survival.

7.2.1 Karnofsky function assessment.

7.2.2 Subjective assessment.

7.3 Local Tumor Response.

The rate of regression of the primary tumor and regional nodes under radiotherapy and at each assessment will be determined by measurements of the primary tumor and any palpable nodes, in maximum dimensions and two dimensions at right angles to determine tumor volume if possible; otherwise by subjective assessment of percentage regression. Assessment will be recorded just prior to Day 1, at 5000 rad, immediately after treatment, following surgery, if done, or boost radiotherapy, and at each follow-up visit. While three dimensions for tumor volume determinations should be recorded, routine assessments will use two dimensions. Assessment will be as follows:

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

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

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

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

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

7.4 Response of regional node metastasis.

7.5 Incidence of distant metastasis.

7.6 Incidence of local recurrence.

7.7 Evaluation of acute and late response of normal tissue (Appendix III).

8.0 POST-TREATMENT EVALUATION

Parameters to be recorded at each follow-up evaluation while on study include:

8.1 Medical history data (see section 4.1), including Karnofsky Scale.

8.2 Physical examination.

8.3 Laboratory tests, as indicated.

8.4 Imaging procedures, as indicated.

8.4.1 Liver function tests or scan.

8.4.2 Bone survey or scan.

8.4.3 Brain Scan.

8.5 Summary of Evaluation Parameters.

	Pretreatment	At completion	At Follow-up
History and Physical	x	x	x
Performance Status	x	x	x
CBC, Differential, Platelets	x		a
Urinalysis	x		a
Blood Chemistries	x		a
Liver Enzymes	x		a
Cardiopulmonary Assessment	a		
Chest x-ray	x		a
Special Procedure*	a	a	a
CT Scan	x	a	a
Ophthalmologic Exam	b		b
Metastatic Surveys (liver, bone brain, etc.)	a		a

* As indicated to evaluate disease (tomograms, endoscopic exams, soft tissue or mandible radiographs, etc.)
a - If clinically indicated.
b - Prior to treatment and yearly thereafter.
x - Required, consistent with good medical practice.

9.0 FOLLOW-UP SCHEDULE

Patients receiving pion radiotherapy will receive an annual physical examination by a radiation oncologist at the study center in Albuquerque or at a regional clinic closer to the patient's home. Deaths of patients treated with either pion radiotherapy or conventional therapy will be reported. The purpose of follow-up assessments is to determine:

9.1 Gross tumor response to treatment.

9.2 Time of distant spread and involved organs and nodes.

9.3 Long-term normal tissue effects of radiotherapy.

9.4 Time and site of local recurrence (if any) as accurately as possible.

9.5 Patient functional status during survival.

9.6 Time of survival in years.

9.7 The first day of definitive treatment is considered Day 1. Follow-up assessments should be scheduled within two weeks of the specified times and will be reported:

9.7.1 One month after treatment, then every three months for 12 months counting from Day 1.

9.7.2 Every six months for the next four years (when patient survival time reaches five years after Day 1).

9.8 If a study patient cannot return to the Study Center in Albuquerque, arrangements will be made to have him examined at another hospital or by his private physician and a report of this examination submitted. The following information will be recorded on the follow-up form at each visit (unless indicated otherwise):

9.8.1 Brief interim history, to include the following information:

9.8.1.1 Xerostomia.

9.8.1.2 Local pain.

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

9.8.1.4 Evidence of soft-tissue necrosis.

9.8.1.5 Evidence of bone necrosis.

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

9.8.1.7 Recovery of normal speech in the absence of laryngectomy.

9.8.1.8 Performance status.

9.8.1.9 Weight.

9.8.1.10 Acute and late response of normal tissue (see Appendix IV).

9.8.2 Physical examination: (same as 4.2).

9.8.3 Performance status (Karnofsky function assessment).

9.8.4 Laboratory tests, as indicated.

9.8.5 Imaging procedures, as indicated (same as 8.4).

9.8.6 Ophthalmologic exam to assess lens opacity (annually).

9.8.7 Progress toward endpoints (complications, tumor response, etc.) will be recorded and reported at each follow-up visit. If a recurrence develops, a biopsy should be taken and the date of recurrence should be fixed as closely as possible. Patients receiving pion radiotherapy will receive an annual physical examination by a Study Center radiation oncologist at the Study Center in Albuquerque or at a regional clinic closer to the patient's home.

10.0 PATHOLOGY

10.0 Pathology data will be derived from:

10.1.1 Biopsy Specimens. Biopsy specimens will be examined by pathologists at the participating institutions to substantiate the diagnoses. Representative slides for patients entered onto the study will be forwarded to RTOG Headquarters for review by the study pathologist. Copies of biopsy reports will be submitted to RTOG Headquarters and the referring and/or follow-up physician.

10.1.2 Surgical Specimens. Any tissue surgically removed from anatomic sites will be examined by pathologists at the participating institutions where the surgery was performed. A description of the surgical specimen and microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

10.1.3 Autopsies. Autopsies should be performed on all study patients by pathologists at the participating institutions. The postmortem study should include a description of irradiated tissues and pattern of tumor spread. Autopsy reports and representative microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist, with detailed anatomic description of the sites where specimens were obtained for correlation of pion dose and pathological changes.

11.0 FORMS

A copy of each study form must be submitted to RTOG Headquarters. Data will be recorded on standard forms to be supplied to each participating institution. The following records will be generated by the study team and participating institutions for storage, retrieval, and analysis:

11.1 RTOG initial registry form (submitted for both eligible and ineligible patients entering each participating institution).

11.2 On study form.

11.3 Treatment prescription.

11.4 Localization films.

Localization films of each field will be taken and sent to the RTOG Office in the first week of therapy together with a copy of the treatment plan.

11.5 Treatment summary form:

11.5.1 Radiation therapy administered (type of energy, daily schedule of treatment, maximum dose, complications during radiation therapy, a description of the lesion at the end of treatment, patient's weight at the end of treatment, performance at end of treatment, complications following therapy and their management, copies of port films and isodose curves, etc.).

11.5.2 Operative procedures and findings, if applicable (extent of disease, presence of metastases, type and extent of surgery performed, etc.).

11.5.3 Postoperative data (complications following surgery, patient weight at time of discharge, performance at time of discharge, etc.).

11.5.4 Drugs administered, if any (a description of type and dose of any drugs administered, duration, and purpose, including any chemotherapy administered in the event of lack of tumor control).

11.6 Follow-up Assessment Form (see Section 9.0).

11.7 Pathology Forms (see Section 10.0)

11.8 Summary of Forms Submission.

Form	Due
Initial registry	Within two weeks of evaluation
On study form Study entrance form Radiotherapy prescription Copies of localization films Pathology slides and reports	Within two weeks of randomization
Treatment summary form Copy of radiotherapy record Copy of boost fields Isodose distribution	Within two weeks of completion of radiotherapy
Follow-up assessment	Within two weeks of times in 9.7
Surgery form Pathology slides and report	Within one month of surgery
Death form	Within one month of death

12.0 ADDITIONAL THERAPY ALLOWED

Therapy is to be administered as detailed in section 6.0. Subsequent therapy shall proceed at the discretion of the patient's responsible physician. Indications for subsequent therapy and the therapy performed should be documented in the patient's follow-up records.

13.0 STATISTICAL CONSIDERATIONS

The two main endpoints of this study are local control and survival. Local control is easier to evaluate in that it requires less follow-up (in this disease the majority of treatment failures will be apparent by 18 months after treatment) and requires fewer patients to detect improvements. The following table shows that to be relatively certain of detecting 40% local control for pion-irradiated patients over a 20% rate for conventionally irradiated patients, a total of 150-180 patients will be needed.

Based on available literature and their experience, members of the Committee on Human Trials of Pion Radiation Therapy have determined that a cumulative 5-year survival rate of approximately 15% is currently experienced by patients eligible for this study. They further felt that an improvement of 100% (or survival of about 30%) should be sought for patients assigned to pion radiotherapy.

The patients in the local control comparison will give a somewhat lower probability of detecting a 30% vs. 15% 5-year survival rate for the pion- and photon-irradiated groups.

PROBABILITY OF DETECTING

(A) A Doubling of LOCAL CONTROL RATE Number of Patients/Arm		(B) A Doubling of 5-Year Survival Rate Average Follow-Up	3-Yr.	4 Yr.	5 Yr.
70	88%		55%	67%	74%
80	91%		66%	74%	82%
90	94%		75%	84%	88%
100	95%		81%	89%	92%

The survival calculations assume a negative exponential distribution giving rise to log-death-rates which are approximately normally distributed. For both endpoints, a one-sided 5% test of significance is used.

14.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, Food and Drug Administration, and National Cancer Institute regulations requiring submission to the institutional human experimentation committee and the use of procedures for obtaining and recording informed consent will be followed. A patient may be removed from the study at any time if the study is not in the best interest of the patient. A patient may withdraw voluntarily from the study at any time, as will be indicated in the consent form (See Appendix V).

REFERENCES

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2. Fletcher, G.H., MacComb, W.S., Braun, E.J.: Analysis of sites and causes of treatment failures in squamous cell carcinoma of the oral cavity. Am J Roentgenol 83 March, 1960.

3. Clinical staging system for carcinoma of the oral cavity. Chicago, American Joint Committee for Cancer Staging and End Results Reporting, 1968.

4. Chen, K.Y., Fletcher, G.H.: Malignant tumors of the nasopharynx. Radiology 99:165, 1971.

5. Fletcher, G.H., Million, R.R.: Malignant tumors of the nasopharynx. Am J Roentgenol 93:44, 1965.

6. Clinical staging system for carcinoma of the pharynx (nasopharynx, oropharynx, and hypopharynx). Chicago: American Joint Committee for Cancer Staging and End Results Reporting, 1965.

7. Dalley, V.M.: Cancer of the laryngopharynx. J Laryng and Otol 82:407-419, 1969.

8. Kligerman, M.M., Smith, A.R., Yuhas, J.M., Wilson, S., Sternhagen, C.J., Helland, J.A., Sala, J.M.: The relative biological effectiveness of pions in the acute response of human skin. Int J Rad Onc Biol Phys 3:335-339, 1977.

9. Kligerman, M.M., Sala, J.M., Wilson, S., and Yuhas, J.M.: Investigation of pion treated human skin nodules for therapeutic gain. Int J Rad Onc Biol Phys 4:263-265, 1978.

APPENDIX I

STAGING OF CANCER AT HEAD AND NECK SITES

Staging. Staging for this protocol is derived from the AJC clinical staging system. The assessment of the extent of the primary tumor will usually be based on inspection and palpation of the oral cavity, pharynx, and neck. Radiographic studies may be important in assessing bone invasion. Palpation of the neck is necessary to establish clinical suspicion of the presence or absence of cervical lymph nodes. In clinical evaluation, the actual size of a nodal mass should be measured and allowance made for intervening soft tissues. It is recognized that most masses over 3 cm in diameter are not single nodes but confluent nodes or tumor in soft tissues of the neck. Midline nodes are considered homolateral nodes.

American Joint Committee for Cancer Staging and End Results Reporting (1978)

Oral Cavity

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

Primary Tumor (T)

TX	No available information on primary tumor
T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Greatest diameter of primary tumor 2 cm or less
T2	Greatest diameter of primary tumor greater than 2 cm but not greater than 4 cm
T3	Greatest diameter of primary tumor 4 cm or greater
T4	Massive tumor greater than 4 cm in diameter with deep invasion to involve antrum, pterygoid muscles, base 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

T0 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

T3 Massive tumor invading bone or soft tissue of neck

Nodal Involvement (N)

NX Nodes cannot be assessed

N0 No clinically positive nodes

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

N2 Single clinically positive homolateral node greater than 3 cm but not greater than 6 cm in diameter or multiple clinically positive homolateral nodes, none over 6 cm in diameter

N2a Single clinically positive homolateral node greater than 3 cm but not greater than 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 greater than 6 cm in diameter

N3b Bilateral clinically positive nodes (in this situation, each side of the neck should be staged separately; that is, N3b: right, N2a; left, N1)

N3c Contralateral clinically positive node(s) only

Distant Metastasis (M)

MX Not assessed

M0 No (known) distant metastasis

M1 Distant metastasis present

Specify_____

Specify sites according to the following notations:

Pulmonary - PUL

Osseous - OSS

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

STAGE GROUPING

Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1 or T2 or T3, N1, M0
Stage IV	T4, N0 or N1, M0
	Any T, N2 or N3, M0
	Any T, Any N, M1

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

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 hyperplasis. 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 3 mm deep, carious lesions are not in close proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examination should show at least 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 and restoration of the remaining teeth as required. The patients are instructed for dental prophylaxis and utilize custom-made fluoride carriers.

GROUP 4

Includes those whose dental hygiene is good. This includes patients who do not have severe malocclusion and in whom 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 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 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 molded 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 is necessary.

RESULTS

In the 5-1/2 year program at the M. D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Group 3 and 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 utlimately be necessary.

APPENDIX IV

ACUTE NORMAL TISSUE REACTION GRADES

1. Skin
   - 0 - Nil
   - 1 - Erythema
   - 2 - Dry Desquamation
   - 3 - Moist Desquamation
   - 4 - Acute Necrosis

2. Oral-Pharyngeal Mucosa
   - 0 - Nil
   - 1 - Injection
   - 2 - Patchy Pseudo-Diphtheritic Membrane
   - 3 - Confluent Pseudo-Diphtheritic Membrane
   - 4 - Ulceration

3. 0 - Nil
   - 1 - Distortion of sense of taste without Xerostomia
   - 2 - Mild Xerostomia
   - 3 - Moderate Xerostomia
   - 4 - Severe Xerostomia
   - 5 - Acute Salivary Gland Necrosis

4. 0 - Nil
   - 1 - Mild to Moderate Diarrhea, No Tenesmus
   - 2 - Diarrhea with Mucous or Mild to Moderate Tenesmus
   - 3 - Diarrhea with Bleeding or Severe Tenesmus
   - 4 - Acute Necrosis

   4a. Proctoscopic Findings
   - 0 - Nil
   - 1 - Injection
   - 2 - Dusky Mucosa
   - 3 - Edema
   - 4 - Punctate Hemorrhage
   - 5 - Gross Bleeding

5. GU Tract Symptoms
   - 0 - Nil
   - 1 - Mild Dysuria, Nocturia < 3
   - 2 - Moderate Dysuria, Nocturia $> 3 < 5$
   - 3 - Severe Dysuria, Bladder Spasms, Nocturia > 5
   - 4 - Gross Hematuria

6. Epilation
   - 0 - Nil
   - 1 - < 20% of Field
   - 2 - < 50% of Field
   - 3 - > 50% of Field
   - 4 - Complete Field

APPENDIX IV

[redacted]

Organ/Tissue	0	1 Mild	2 [redacted]	3 [redacted]	4 Life Threatening	5*
SKIN	None	Slight atrophy Pigmentation change Some hair loss	[redacted] atrophy Moderate telangiectasia Total hair loss	[redacted] 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	
T	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	

Grade 5: Death directly related to radiation late effect

APPENDIX V

PATIENT CONSENT FORM FOR
RADIATION TREATMENT OF HEAD AND NECK CANCER*

PATIENT'S NAME: _____

ADDRESS: _____

HOSPITAL/CLINIC: _____

HOSPITAL/CLINIC I.D. NUMBER: _____

1. I, _____ (Name of Patient), agree to take part in a research study to test the use of radiation to treat cancer of the head and neck. Dr. Steven E. Bush, Dr. _____ (Name of Physician), and doctors they have chosen will do this study. Persons helping them will be supervised by a doctor at all times while treatment is being given.

2. The treatment to be given to me has been described to me by Dr. _____. It is as follows:

   a. I might receive x-ray or cobalt treatments to my head and neck. These treatments might be given to me at the _____ (Name of Institution).

   b. I might receive negative pi meson (pion) treatments to my head and neck. These treatments might be given to me at the Los Alamos Meson Physics Facility, Los Alamos, New Mexico.

   c. Some radioactive material might be inserted in the area of my tumor, and then removed after several days.

   d. I might have an operation after the treatments described above.

   e. If I agree to take part in the study, I must agree to go to Albuquerque and Los Alamos, New Mexico, for tests so that my doctors can plan the best possible treatment for me.

   f. If I am chosen for pion treatment, I must stay the needed time (about eight weeks) in Los Alamos for treatment.

   g. I must agree to return to the University of New Mexico Cancer Research and Treatment Center in Albuquerque for needed follow-up exams, if I am chosen for pion treatment.

   h. I understand that I will be chosen by chance for either x-ray, cobalt or pion treatment, and that my doctors cannot tell me ahead of time which treatment I will be chosen to receive.

*Sample Consent Form Submitted by the Study Chairman.

3. Dr. _____ has told me that I might not feel well after these radiation treatments. Some of the things that might happen to me are:

a. My skin might get red and peel in the treatment area.

b. I might have pain or swelling in the treatment area.

c. I may get cavities in my teeth.

d. If the doctor and a dentist say that my teeth are bad, some or all of my teeth may have to be pulled before I can be treated.

e. I may lose hair in the treatment area.

f. I may have a cough, trouble breathing, a sore throat and trouble swallowing. This is usually temporary.

g. I may have dryness or too much moisture in my mouth and throat.

h. I may lose my ability to taste food, although this usually goes away after treatment.

i. I may have a narrowing, sores or openings in the linings of my mouth or throat. These may or may not go away. I may need an operation to help those which do not go away.

j. I may need an operation after my radiation treatment which could result in a permanent loss of voice.

k. I could get weakening of parts of my body or be unable to move them, although this is not expected to happen.

l. I may lose bone or muscle in the treatment area, although this is not expected to happen.

m. The number of my blood cells might be less. This could make it easier for me to get a disease caused by germs, but my blood will be tested often so that any problems can be treated quickly. This would be rare.

n. Even if my blood cells do not become fewer, it might be easier for me to get a disease caused by germs and to run a fever.

o. I may later get a cancer of the thyroid, although this is not expected to happen, especially in people over 45.

p. I might get cataracts (clouding of the lenses) in my eyes. This is not expected, but if it does happen it can be corrected by an operation.

4. Dr. _____ has told me about the good things this research study might do for me and for other people. It will help to find out which kind of radiation is better in controlling head and neck cancer.

5. Dr. _____ has told me about other treatments for me:

   a. An operation before x-ray or cobalt treatment;
   b. An operation alone;
   c. An operation, x-ray, or cobalt treatment and drugs;
   d. An operation and drugs;
   e. X-ray or cobalt treatment and drugs.

6. Dr. _____ will answer any questions I have during the treatment.

7. I know that the treatment could harm me. No one has said that it wouldn't. I can stop treatment at any time I want to.

8. Dr. _____ is in charge of my treatment. He can change the treatment at any time, or stop it.

9. If my body is injured by the research treatment, more than or different from that explained above, I understand that any emergency medical care I need will be given to me at no cost, but I will not be paid any money. Payment for medical costs will not continue after the emergency treatment is finished.

10. I understand that by signing this paper I am not giving up my legal rights. State laws exist which may help people who think they have been treated carelessly. For information, write or call the Risk Management Division, Room 24, Lamy Building, Santa Fe, New Mexico 87503.

Date: _____ Time: _____ Place: _____

Signed: _____ Witness: _____

_____ Witness: _____
(Parent or Guardian When needed)

Original: Patient Chart
cc: Patient
RTOG Headquarters

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