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RTOG 78-28: Revisions/Clarifications - September 11, 1979

713036

The following revisions have been made:

Schema, Item C will read as follows:

> Minimum of 3500 peak pion rad at 100 rad/day calculated at the 80% isodose line (Maximum of 4375 peak pion rad at 125 rad/day at 100% isodose).

The above revisions also apply to Section 6.2 Pion Therapy, Paragraph I.

[redacted] to be attached to the front of the above [redacted] named protocol.

[redacted] SIGNED FOR [redacted]

1086327

RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-28

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

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Activated: June 1, 1979
Current Edition: June 1, 1979

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

SCHEMA

Stratify

- Region
  - Oral Cavity
  - Oropharynx
  - Nasopharynx
  - Hypopharynx
- Stage
  - III
  - IV

RANDOMIZE

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

a. 6600 rad/6½-7⅓ wk to 7500 rad/7½-9 wk.

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

c. Minimum of 3300 peak pion rad at a minimum of 85 peak pion rad/day. The minimum dose is approximately 2 cm peripheral to the 95% isodose line.

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 and Interstitial Irradiation	Patients Salvaged by Surgery (2 years)	Ultimate Failure
Anterior 2/3 Tongue	T1	3/52 (5.7%)	---	3/48 (6%)	0/4 (0%)	1/33 (3%)	6.5%
	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 Mouth	T1	1/49 (2%)	0/10 (0%)	1/31 (3%)	0/8 (0%)	1/1 (100%)	0/0%
	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	No Surgical Salvage
Lower Gingiva	14	0/4	0/5	3/5	
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
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 jugulodigastric, 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-third 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). However, survival of those few patients with Stages I and II tumors may be relatively good (50 to 70 percent, according to the same sources).

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 overcomes 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. In contrast, neutrons, which have no charge, deposit dose in tissue exponentially, similarly to dose absorption of the gamma rays of cobalt.

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).

An analysis of 52 evaluable tumors in 20 patients (including those in the skin metastases series) treated with pions only and followed for 3 to 22 months showed 42 tumors completely regressed, 3 tumors partially regressed, and 7 tumors did not respond, although 5 of the 7 showed no growth for 10 months (10). A more recent 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 relatively mild, compared to those which would be expected with conventional radiation for similar tumor response. No patient receiving treatment to head and neck fields has exhibited any serious untoward reaction over observation times ranging up to 26 months (11).

It is estimated that some 60,000 persons 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 improves 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 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 or IV (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 or IV (see Appendix I).

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. Kligerman (preferred 505/277-3539 or 505/667-7392 in Los Alamos) 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. Kligerman or his designee at the pion facility will complete and submit the on study form and will phone RTOG Headquarters 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. Kligerman 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 6½ to 7½ weeks while the maximum tumor dose to the boosted volume will not exceed 7500 rad in 7½ - 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 6½ to 7½ weeks (7½ - 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 a 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 1½ 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 which 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 node becomes mobile after radiation and primary is controlled by 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 3300 minimum peak pion rad at a distance at least 2 cm from the gross tumor margin and which will be 2 cm from the 95% isodose line. 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. If 75% or more of the larynx is in the target volume, the larynx will be blocked after it has received a maximum of 3000 peak pion rad. The daily minimum tumor dose will be 85 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

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 Status.

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.

	Pre-Treatment	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 Study Center 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 Immediately after treatment, then monthly for six months counting from Day 1.

9.7.2 Every three months for the next 18 months.

9.7.3 Every six months for the next year (when patient survival time reaches three years after Day 1).

9.7.4 If data analysis warrants, patients will continue to be followed at six-month intervals until survival reaches five years after Day 1.

9.8 If a study patient cannot return to the participating hospital where he was entered in the study, 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

10.1 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 (see Appendix V). Autopsy reports and representative microscopic slides will be forwarded to RTOG Headquarters for review by the study pathologist.

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 or 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.). Isodose distributions should be attached.

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 report	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

11.0 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.

12.0 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-irradiation patients over a 20% rate for conventionally irradiated patients, a total of 150-180 patients will be needed.

Based on available literature and their own 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		(B) A Doubling of 5-Year Survival Rate			
Number of Patients/Arm		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.

13.0 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 VI).

REFERENCES

1. Chu, A., and Fletcher, G.H.: Incidence and causes of failure to control by irradiation the primary lesions in squamous cell carcinomas of the anterior two-thirds of the tongue and floor of mouth. Am J Roentgenol 117:503-508, 1973.

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

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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., and 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.

10. Kligerman, M.M., von Essen, C.F., Khan, M.K., Smith, A.R., Sternhagen, C.J., and Sala, J.M.: Experience with pion radiotherapy. Cancer (in press).

11. Kligerman, M.M., Wilson, S., Sala, J., von essen, C., Tsujii, H., Dembo, J., and Khan, M.: Results of clinical applications of negative pions at Los Alamos. In Proceedings of the Third Meeting of Fundamental and Practical Aspects of the Application of Fast Neutrons and Other High LET Particles in Clinical Radiotherapy, Pergamon Press, Oxford (in press).

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 (1977)

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

Primary Tumor (T)

TX	No available information on primary tumor
T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Greatest diameter of primary tumor less than 2 cm
T2	Greatest diameter of primary tumor 2 to 4 cm
T3	Greatest diameter of primary tumor more than 4 cm
T4	Massive tumor greater than 4 cm in diameter with deep invasion to involve antrum, pterygoid muscles, root of tongue, or skin of neck

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

T4 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 less than 3 cm in diameter

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

- N2a Single clinically positive homolateral node 3 to 6 cm in diameter
- N2b Multiple clinically positive homolateral nodes, none over 6 cm in diameter

N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s)

- N3a Clinically positive homolateral node(s), over 6 cm in diameter
- N3b Bilateral clinically positive nodes (in this situation, each side of the neck should be staged separately; that is, N3b: right, N2a; left, N1)
- N3c Contralateral clinically positive node(s) only

Distant Metastasis (M)

MX Not assessed

M0 No (known) distant metastasis

M1 Distant metastasis present

Specify _____

Specify sites according to the following notations:

Pulmonary	PUL
Osseous	OSS
Hepatic	HEP
Brain	BRA
Lymph Nodes	LYM
Bone Marrow	MAR
Pleura	PLE
Skin	SKI
Eye	EYE
Other	OTH

STAGE GROUPING

Stage I	T1 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 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 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

Include 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

Include 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 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

ACUTE/LATE EFFECTS SCORING

Normal Tissue Reaction Grades

1. Skin

00 Nil
01 Threshold erythema
02 Brythema < ½ field
03 Erythema ≥ ½ field
04 Dry desquamation < ½ field
05 Dry desquamation ≥ ½ field
06 Moist desquamation < ½ field
07 Moist desquamation ≥ ½ field
08 Small necrotic ulcer or slough
09 Massive acute skin necrosis
10 Unknown

2. Oral-Pharyngeal Mucosa

0 Nil
1 Injection
2 Patchy pseudo-diphtheritic membrane
3 Confluent pseudo-diphtheritic membrane
4 Ulceration
5 Unknown

3. Salivary Glands

0 Nil
1 Transient aberration of taste or salivation
2 Temporary suppression of salivation with dry mouth
3 Partial loss of taste, persistent lack of saliva
4 Complete loss of taste; nonfunctioning saliva gland
5 Complete obliteration of salivary gland
6 Extensive replacement fibrosis
7 Necrotic ulcer
8 Massive necrosis
9 Unknown

LATE EFFECTS

0	None
1	Lymphedema
2	Fibrosis
3	Pain
4	Ulcer
5	Pneumonitis
6	Pericarditis
7	Necrosis
8	Trismus
9	Xerostomia
10	Chronic enteritis
11	Fistula
12	Myelitis
13	Atrophy
14	Induced tumor
15	Other (specify)

APPENDIX V

AUTOPSY PROTOCOL FOR PATIENTS TREATED WITH PION RADIATION

Histopathological data on the effects of pi mesons on normal as well as neoplastic tissues is still not extensive. For this reason these patients have enormous clinical research importance. This communication is designed to explain the basic questions we would like to try to answer and to serve as a guideline to help you in obtaining the most appropriate tissues as easily and efficiently as possible. We believe that a relatively small group of selectively localized blocks will yield more information than numerous random tissue samples.

Basically four types of specimens need to be collected of which two deal with the neoplasm per se and two with normal tissues from the treatment field. In the first place you will naturally want to assess the effects of therapy on the neoplasm within the central portion of the treatment field. Secondly it will be desirable to compare tissues from this area with those more peripherally situated at or near the margins of the treatment fields. This information will allow the therapists and physicists to assess the accuracy of localization of the field and to draw conclusions relative to dosimetry on the basis of semiquantitative histopathology.

Radiation effects upon normal tissues and organs are equally important because of potential complications of therapy. Once again there is a need to obtain separate specimens from within the treated volume and others from similar but peripheral organs or tissues that were calculated to have received a relatively low dose of radiation.

Initially we felt that the pathologist, provided with the therapy chart, could select appropriate blocks on the basis of his own judgment. In practice this has not been the case since the details of therapy, while recorded in the chart, have seldom been collated into a workable form, i.e., size and shape of fields, relative dose levels etc.

Thus, on the basis of meetings with the Human Trials Committee it was decided that the pathologist must be provided with a simplified "map" that will enable him to obtain proper sections with confidence in the course of performing his usual autopsy procedure. It is clear that this document can only be prepared by the radiation therapist and physicists during or at the conclusion of the patient's therapy.

The accompanying form includes an extremely simplified summary of therapy details together with fairly specific suggestions for tissue sampling. These suggestions are broken down into four categories as explained: 1) Several blocks from the epicenter of the treated tumor; 2) Blocks from the perimeter of the tumor; 3) Blocks from organs situated within the treated volume; 4) Blocks from tissues or organs intercepting radiation but external to the treatment field per se. A set of lettered labels is available corresponding to individual tissue sites in the lettered column as identified by the radiation therapist. The center of the form has been left blank for line drawings by the therapists. These drawings might indicate external landmarks such as tattoos or represent internal cross sections to include metal clips etc. (Initially we attempted to construct anatomically precise horizontal line drawings for each tumor included in the pi meson protocols but believe there is too much individual patient variability with regard to tumor size, configuration and orientation of treatment fields to make this practical).

Please be assured that we will share any information generated by these studies as they pertain to this patient or to the effects of pi mesons on tissues in the most general sense. As in the case of the radiation therapists, there are pathologists from many institutions involved and we sincerely wish this to be a mutually informative effort with wide dissemination of information and findings.

PATIENT'S NAME: _____

SUMMARY OF THERAPY:	Total Dose	Date Completed	Adjuvant Chemotherapy?
High LET	_____	_____	
Low LET	_____	_____	
Other	_____	_____	

RADIATION THERAPIST: _____

PHYSICIST: _____

BLOCKS

T_C (Tumor, Central Treatment Area)

T_P (Tumor, Peripheral Treatment Area)

	OTHER SITE	ESTIMATED DOSE
A	_____	_____
B	_____	_____
C	_____	_____
D	_____	_____
E	_____	_____
F	_____	_____
G	_____	_____
H	_____	_____

T_C	A
T_C	B
T_C	C
T_C	D
T_P	E
T_P	F
T_P	G
T_P	H

APPENDIX VI

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. Morton M. Kligerman, 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 lining 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