RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-02

A PROSPECTIVE RANDOMIZED PHASE III CLINICAL TRIAL EVALUATING THE USE OF POST-OPERATIVE ADJUVANT RADIOTHERAPY IN THE TREATMENT OF PATIENTS WITH CUTANEOUS MELANOMA OF THE HEAD AND NECK

ECOG (R9302)

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SCHEMA

Surgery

STRATIFY

Extracapsular Extension
1. No
2. Yes

Prior Systemic Therapy
1. No
2. Yes

Number of Involved Nodes
1. 1-3
2. > 3

RANDOMIZE

Arm 1: Postoperative Radiation therapy
Total Dose 30.0 Gy in five fx:
6 Gy fx twice a week for 2 1/2 weeks.

Arm 2: Observation

Eligibility *(See Section 3.0 for details)*

- Diagnosis of melanoma in pathologically positive node(s)
- Nodes must be above the clavicle
- No contraindications to radiation therapy
- Disease must be completely resected prior to randomization
- KPS $\geq$ 60
- Age $\geq$ 18
- No distant metastasis or prior RT to the head and neck
- Complete recovery from surgery
- Protocol treatment must begin within six weeks of surgery

Required Sample Size: 148

Revised 4/29/94

RTOG Inst. # _____ **Revised 4/29/94**

RTOG 93-02 ***(ECOG R9302)*** **ELIGIBILITY CHECK**

RTOG Case # _____

Other Group Seq. # _____

_____(Y) 1. Has the diagnosis of melanoma of a neck node or nodes been pathologically confirmed?

_____(Y) 2. Is the location of all nodal involvement limited to the area above the clavicles?

_____(Y) 3. Has the patient undergone a complete nodal dissection including parotidectomy if applicable?

_____(Y) 4. Based on the surgical findings and the final pathological evaluation, has all gross tumor been removed with pathologically negative margins?

_____(N) 5. Is the interval between resection and today > 42 days?

_____(Y) 6. Has the patient recovered from surgery to the extent that if assigned radiotherapy, treatment will begin within 42 days of the resection?

_____(N) 7. Is the primary melanoma located in the trunk, extremities, or in the mucosa?

_____(N) 8. Any evidence of distant metastatic disease?

_____(N) 9. Any previous or synchronous head or neck cancer?

_____(N) 10. Any prior radiotherapy to the head or neck?

_____(N) 11. Does the post-operative treatment plan include any systemic therapy or any other therapy other than the assigned protocol option?

_____(≥ 18) 12. What is the patient's age?

_____(≥ 60) 13. What is the KPS?

_____(N) 14. In the opinion of the principal investigator, is the patient's life expectancy considered to be < 6 months?

_____(Y) 15. Has the patient signed a study-specific consent form?

_____ Patient's Name _____ Birthdate

_____ Verifying Physician _____ Sex

_____ Patient ID #_____ Race

_____ Referring Institution _____ Social Security Number

_____ Extracapsular Extension *(no vs. yes)* _____ Zip Code *(9 digit if available)*

_____ Prior Systemic Therapy *(no vs. yes)* _____ Method of Payment

_____ Number of Involved Nodes *(1-3 vs. > 3)* _____Treatment Start Date *(if assigned RT)*

Completed by _____ Telephone# _____

1.0 INTRODUCTION

1.1 Background

There is a general agreement that radiation as definitive management of primary disease is rarely indicated. Complete surgical excision is preferred because the specimen removed as therapeutic intervention is also essential for establishing diagnosis and accurate microstaging to determine the prognosis of the patient. However, firm data are now available showing that surgery alone is insufficient in obtaining regional disease control in a number of subsets of patients. For instance, data of the World Health Organization *(WHO)* Melanoma Registry demonstrate that ~ 40% of patients with cutaneous melanoma of more than 1.5 mm without palpable lymphadenopathy at diagnosis *(Stages II by 1983 American Joint Committee on Cancer Staging System)*[2] develop regional relapse after wide local excision.[4] Local recurrence in also an important treatment failure component after wide excision of > 4 mm lesions.[8] In addition, data from the University of Texas M.D. Anderson Cancer Center[3] and the Sydney Melanoma Unit[6] reveal that 34-50% of patients presenting with palpable lymphadenopathy *(Stage III)* relapse regionally after therapeutic nodal dissection. Although most of patients die as a consequence of distant spread, which usually manifests clinically in less than 2 years after treatment[9], local regional relapses are often refractory to therapy and produce substantial morbidity such as ulceration, disfigurement, and pressure symptoms, Local-regional relapse from cutaneous melanoma of the head and neck is particularly distressing by compression of vital organs. Therefore, prevention of local regional failure would improve the quality of life when this could be achieved with a well tolerated treatment.

1.2 Preliminary Study

Based on the rationale outlined above, a phase II study was initiated at the University of Texas M.D. Anderson Cancer Center in 1983 to address the feasibility and efficacy of elective/adjunctive radiotherapy in the management of patients with cutaneous melanoma of the head and neck region having a high risk for local-regional relapse.[1] Three subsets of patients were enrolled into this study. These were patients with stage II lesions after wide local excision *(group 1)*, those with stage III disease after wide local excision and therapeutic nodal dissection *(group 2)*, and patients who had primary lesion excised and subsequently underwent therapeutic nodal dissection for regional relapse *(group 3)*.

The radiation schedule was chosen based on the outcome of literature survey. Over the past two decades, a large number of retrospective clinical studies have addressed the effect of fraction size on the response rates of metastatic melanomas. No firm conclusions with regard to the relative importance of the fraction size can be drawn from the literature data because of the heterogeneity of clinical material *(variability in metastatic site, size of metastatic deposit, and radiation dose)*. However, when only the data of cutaneous and lymph node metastasis were extracted, there was a trend in favor of higher response rates in regimens using fraction sizes of 4 Gy or more than those using 2 to 4 Gy.[7] Therefore, a hypofractionated regimen *(6 Gy per fraction twice a week to a total dose of 30 Gy)* was selected for this study. Irradiation was delivered with electrons whenever possible to limit the volume of normal tissues exposed to large dose fractions, and thus the probability of treatment complications.

Table 1: Pattern of Failure after Adjunctive Radiotherapy

STATUS	NED	D	D+N	D+DM	N+DM	D+N+DM	DM Only
Group 1	45	2	1	--	2	--	19
Group 2	13	--	--	2	--	--	13
Group 3	30	1	--	1	1	2	24
TOTAL	88	3	1	3	3	2	56

NED: No Evidence of Disease; D: Dermal Recurrence; N: Nodal Relapse; DM: Distant Metastasis

From January 1983 to December 1991, a total of 156 patients, 117 men and 39 women were enrolled into this phase II study. The age ranged from 16 to 89 years, with a median of 54 years. Ninety eight of 156 patients were alive at the time of analysis. The length of follow-up of these 98 patients ranged from 3 to 112 months, with a median of 33 months. The pattern of failure in each patient group is shown in Table 1. The actuarial local-regional control and survival rates of the whole patient population at 2 and 5 years are summarized in Table 2. Results by patient subset can be summarized as follows:

Group 1. The actuarial local-regional control and survival rates at 2 and 5 years are shown in Table 2. Of 69 patients who were irradiated electively, 60% had > 1.5-4 mm thick and 20 patients had > 4 mm thick lesions. The remaining patients had Clark's level IV lesions of ≤ 1.5 mm. The thickness of the primary lesion had no appreciable influence on local-regional control rates *(86% to 100% 5-year control rates)*. However, as expected, lesion thickness strongly affected the 5-year survival rate, i.e. 100% for ≤ 1.5 mm, 67% for > 1.5-4 mm, and 21% for > 4 mm.

Table 2: Actuarial Local-Regional Control and Survival Rates.

Patient		Local Regional Control		Overall Survival	
Subset	Number	2 years	5 years	2 years	5 years
Group 1	69	94%	89%	85%	57%
Group 2	28	92%	92%	77%	38%
Group 3	59	89%	89%	71%	34%
ALL	156	92%	89%	78%	45%

Groups 2 and 3: Table 2 summarizes actuarial local-regional control and survival rates at 2 and 5 years for these two groups of patients. With the addition of adjunctive radiotherapy the presence of high number of positive nodes or extracapsular extension did not reduce the local-regional control rate. The 5-year actuarial local-regional control rate for patients with > 3 nodes or with extracapsular extension was 90% and that of patients with 1-3 nodes and no extracapsular extension was 89%. The 5-year survival rate of patients with > 3 involved nodes was lower than that of patients with 1-3 positive nodes *(22% vs. 36%)*. However, the presence of extracapsular extension did not influence the survival rate.

The acute tolerance to adjunctive radiotherapy was excellent. The most frequently observed acute reaction is transient parotid swelling, lasting for about a day, after the first radiation fraction. Moist skin desquamation and confluent mucositis of short duration were observed in < 5% of patients. One patient developed surgical wound infection requiring hospitalization. With a median follow-up time of over 30 months, late radiation complications were observed in only three patients. These were moderate neck fibrosis, mild ipsilateral hearing impairment *(30 dB at 4000 Hz and 25 dB at 2000 Hz)*, and transient exposure of external auditory canal cartilage. These radiation-induced side effects developed within 18 months after completion of radiotherapy.

1.3 Proposed Prospective Randomized Trial

The results of the phase II study presented above show that the hypofractionated radiation regimen used is well tolerated by the patients. The local control rates obtained with postoperative radiation were higher than that of the historical groups treated with surgery alone. A phase III trial, however, is needed to determine the true value of adjunctive radiotherapy in reducing the regional relapse rate in patients with cutaneous melanoma.

Patient subsets thought to be suited for this proposed multi-institutional study are those who present with histologically proven nodal involvement at diagnosis and those who experience nodal relapse after having undergone wide local excision of the primary lesion. The overall regional recurrence rate after neck dissection in this population is estimated to be approximately 40%. It is reasonable to expect, based on the results of the phase II trial, that the use of adjunctive radiotherapy would reduce the regional relapse rate to 20%.

2.0 OBJECTIVES

2.1 To evaluate the effectiveness of post-operative hypofractionated radiotherapy in preventing regional failure in patients with pathologically-proven metastatic melanoma in lymph node(s).

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically documented diagnosis of melanoma in node(s). Patients presenting with nodal recurrence after excision of previous primary lesion are also eligible.

3.1.2 Primary may be known or unknown.

3.1.3 Node(s) must be above the clavicle.

3.1.4 All gross cancer must be removed prior to randomization. Margins must be negative. A previous node biopsy does not make the patient ineligible for the protocol as long as a subsequent complete neck dissection or parotidectomy is performed.

3.1.5 No prior history of radiation to the head and neck.

3.1.6 Karnofsky ≥60 and a life expectancy of at least 6 months.

3.1.7 Age of ≥18 years.

3.1.8 No evidence of distant metastases.

3.1.9 A study-specific consent form must be signed prior to entry into this study.

3.1.10 Patient must have recovered completely from surgery.

3.1.11 Radiation must take place within six weeks of surgery.

3.1.12 Patients may have received any number of courses of systemic chemotherapy or biologic therapy prior to surgery.

3.2 Conditions for Patient Ineligibility

3.2.1 Evidence of distant metastases.

3.2.2 Previous treatment with radiation.

3.2.3 Unresectable disease.

3.2.4 Life expectancy <6 months or a Karnofsky status of < 60.

3.2.5 Any previous or synchronous head and neck cancer.

3.2.6 Primary melanoma of mucosa, trunk or extremities.

3.2.7 Local nodal excision only.

3.2.8 Patients whose treatment plan includes post-op chemotherapy or other systemic therapy.

3.2.9 Gross residual disease or positive margins following surgery.

3.2.10 Patients whose condition delays randomization > 42 days *(> 6 weeks)* after resection.

4.0 PRETREATMENT EVALUATIONS

4.1 Complete history and physical examination.

4.2 Chest x-ray and blood chemistry *(CBC, SMA)*.

4.3 CT scan of the head and neck area and other metastatic work-up as indicated.

4.4 Patients will undergo an appropriate nodal dissection either electively for primaries with a high risk of occult nodal metastases *(Clark's level IV and V, thickness ≥ 1.5 mm)* or for clinically positive node(s) along with resection of the primary lesion when applicable. A radical lymphadenectomy is not required. The surgical specimen must be evaluated for the number of nodes removed, the size and number of positive nodes, and the presence or absence of extracapsular extension.

4.5 If radiation portal includes ipsilateral parotid gland and mandible, dental evaluation and routine prophylaxis should be done prior to initiation of adjunctive radiotherapy. If dental extactions are necessary, complete healing *(at least two weeks)* must occur before starting radiotherapy.

5.0 REGISTRATION PROCEDURES *(revised 4/29/94)*

5.1 Randomization

It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases. Patients who meet the eligibility criteria in Section 3.0, sign the consent form, and pass the pretreatment evaluation, may be entered into the study prior to any protocol therapy. Member institutions will phone their respective Cooperative Group headquarters Mondays through Fridays. The following information will be required at the time of patient entry:

- Institution's Name and RTOG Institution Identification Number
- Patient 's name and ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- Stratification Information
- IRB Approval Date
- Name of Radiation Oncologists
- Demographic Data
- Treatment Start Date ***(must be within 6 weeks of surgery)***

5.2 **ECOG** (617) 632-2022, 8:30 am - 4:30 pm, Eastern Time

RTOG (215) 574-3191, 8:30 am - 5:00 pm, Eastern Time

5.3 The Cooperative Group will then phone RTOG Headquarters, Monday-Friday, between 8:30 a.m. to 5:00 p.m. ET and RTOG will assign the treatment option and RTOG case number.

5.4 After receiving the case number and treatment assignment, the Cooperative Group will phone their registering institution and relay this information.

5.5 The case number and treatment option will be confirmed by mail. RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case. The participating Group should then forward a copy of the calendar and the confirmation to the participating institution.

6.0 RADIATION THERAPY

6.1 ARM 1

6.1.1 **Those assigned to receive radiation therapy (Arm 1) will start treatment no later than 6 weeks *(42 days)* after surgery.** The dose to deliver is 6.0 Gy per fraction, two treatment days per week *(preferably Monday and Thursday or Tuesday and Friday)* to a total of 30.0 Gy in five fractions in 2 1/2 weeks. Day of treatment must be clearly indicated in the treatment record.

6.1.2 *Equipment*: linear accelerators with appropriate photon and electron energies or Cobalt machines must be used.

6.1.2.1 Photon energies of 1.25 to 6 MeV or electron energies from 6-15 MeV are allowed. *Treatment should be given with electrons whenever feasible.* The electron energy should be appropriate for the depth of the tumor and surgical bed, e.g., 6-9 MeV for primary tumor bed, 12-15 MeV for parotid and upper neck nodes, and 9 MeV for mid- and lower jugular and supraclavicular nodes. Photons may be used in selected cases, e.g., opposed AP-PA fields to encompass subdigastric, mid and lower jugular and supraclavicular nodes when the primary lesion is situated at the lateral aspect of the mid-portion of the neck with positive mid-jugular nodes.

6.1.3 Treatment distance must be ≥ 80 cm SSD *(or SAD for isocentric techniques)*.

6.2 Localization Requirements

6.2.1 *Simulation*: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Radio-opaque markers should be used to delineate the extent of nodal disease and scar(s).

6.2.2 *Verification*: Beam verification *(port)* films must be obtained for each photon field. This should be done whenever any field adjustments are made. Port films of each field must be submitted to RTOG Headquarters.

6.2.3 *Photographs*: Polaroid photographs of the patient in the treatment position must be provided. The borders of electron field(s) should be delineated.

6.3 Target Volume

6.3.1 Fields must include the primary tumor bed *(except for instances of an unknown primary or for primary lesions excised ≥ 1 yr)* and ipsilateral neck nodes down to the clavicle. The target volume thus includes parotid nodes for lesions of frontal, preauricular, temporal areas, auricle, and cheek and suboccipital nodes for lesions situated behind the mastoid.

6.3.2 Fields borders encompass nodal areas and tumor bed with at least 2 cm margins for lesions of 1.5 - 4.0 mm, or 3 cm margins for thicker lesions. Bolus should be used to prevent underdosage to tumor bed when electrons of ≤ 9 MeV are used. When it is necessary to irradiate parotid lymph nodes, it is recommended to use a lead alloy-containing intraoral stents to limit the dose delivered to the tongue and oral tissues.

6.3.3 *Field set up*: The vast majority of target volumes can be encompassed with two abutting electron fields. Intraparotid and upper neck nodes are encompassed in one field that is similar to that used for treating primary tumors of the parotid gland. This field also covers most primary tumor beds of lesions arising at preauricular, lower temporal areas, auricle, and cheek. The mid and lower neck nodes are encompassed in an adjoining appositional field. If the site of the primary lesion is outside the boundary of the "parotid" field, a third adjoining field is added to irradiate the tumor bed. The junction between the abutting fields is moved 1 cm after the 2nd and 4th treatments to prevent dose inhomogeneity and thus minimize the risk of fibrosis. Document junction changes in treatment chart.

6.4 Dose Specification

6.4.1 *Photon Beam*:

a. For two opposed coaxial equally weighted beams: on the central ray at midseparation of beams.
b. For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
c. For single beam: on the central ray at the center of the target area.
d. For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
e. The dose inhomogeneity across target volume should be < 10%.

6.4.2 *Electron Beam*: The protocol dose shall be prescribed at the depth of maximum dose. The energy and field size shall be chosen so that the target volume is encompassed within 90% of the prescribed dose.

6.4.3 *Isodose Distributions*: A cumulative isodose distribution at the level of the tumor center is required.

6.5 Time and Dose Modification

6.5.1 Alteration to prescribed fractionation or treatment days must be documented in the treatment record. Due to the short duration of prescribed treatment, any variation in time or dose will be considered as such in the final quality assurance review.

6.6 Critical Structures

6.6.1 The maximum permissible dose to the spinal cord is 24 Gy.

6.7 RTOG Quality Assurance

6.7.1 The protocol course of treatment is 2.5 weeks, thus eliminating the initial *(on-study)* review. The following items are required at the completion of RT: simulation and portal verification films of all fields treated, the calculation form, daily treatment record, isodose distribution and polaroid photo *(see Section 12.0)*.

6.8 Adverse Reaction Reporting *(added 4/29/94)*

6.8.1 All fatal toxicities *(grade 5)* resulting from protocol treatment must be reported by telephone to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

6.8.2 All life threatening *(grade 4)* toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman to RTOG Headquarters Data Management and the primary Study Chairman within 24 hours of discovery.

6.8.3 Appropriate data forms, and if requested a written report, must be submitted to RTOG Headquarters within 10 working days of the reported incident.

6.8.4 Reports and forms must be sent to RTOG via the respective Group offices. See Section 12.2.

6.8.5 *ECOG Toxicity Reporting Guidelines*

All toxicities should be coded according to the RTOG Acute Radiation Morbidity Scoring Criteria *(Appendix IV)*.

Written Adverse Drug Reaction reports are to be submitted ONLY on the Adverse Reaction *(ADR)* Form for Investigational Drugs *(Form 391RF)* and the form must be signed by the treating investigator. RTOG will accept this form in lieu of the FDA Adverse Drug Reaction *(ADR)* Form 1639. All ADR reports are to be accompanied by copies of supporting documentation. In addition, your institution's IRB must also be notified.

This protocol contains no investigational drugs. Toxicities occurring on the treatment arm are to be considered commercial. Events indicated below must be reported to ECOG and the NCI in the manner specified.

For

- Any death while on treatment if clearly related to protocol treatment:
- All unexpected toxicities
- Any increased incidence of a known ADR
- Any life threatening *(grade 4)* toxicities resulting from protocol treatment:

Call ECOG Data Management office within 24 hours of the event. Submit original written ADR form to ECOG Data Management Office within 5 working days of the event. In addition, a copy must be mailed to the Investigational Drug Branch within 10 days.

NCI Mailing Address	ECOG Address:
I.D.B.	ECOG Data Management Office
P.O. Box 30012	ATTN: ADR
Bethesda, MD 20824	303 Boylston Street
NCI Telephone Number:	Brookline, MA 02146-7215
(301) 230-2330	ECOG Telephone Number:
NCI Fax: (301) 230-0159	(617) 632-3610

The ECOG Data Management Office will forward all ADR reports to RTOG.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

The concept from a surgical viewpoint is to remove all gross evidence of disease in nodal and connective tissue in the neck and/or the parotid prior to randomization. The surgical dissection should be accomplished in such a manner as to minimize any complications which would delay the start of radiation more than three to four weeks. Since the incisions and the drainage catheter sites must be included in the fields, the placement of these should be planned so as to minimize the fields of radiation. A previous node biopsy does not make the patient ineligible for the protocol as long as a subsequent complete neck dissection or

parotidectomy is performed. Every attempt should be made to remove all of the nodes at risk for harboring occult disease if the dissection is done electively. It is not required that a radical neck dissection be performed in every patient, in fact, important anatomic structures *(i.e. 11th nerve)* not grossly involved with melanoma should be preserved. A copy of the operative report must be sent to the Principal Investigator. The surgical specimen must be properly oriented for the pathologist so that all nodal levels can be identified. Refer to the following diagram :

9.0 OTHER THERAPY

At the discretion of the treating investigator, additional systemic therapy may be administered **at relapse or progression of disease**. Planned post-operative systemic therapy is not permitted.

10.0 PATHOLOGY *(12/23/94)*

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Patients will be examined weekly. The acute skin and mucosal reactions will be scored according to the RTOG Acute Morbidity Scoring Criteria *(Appendix IV)* during treatment.

11.2 Routine follow-up will be carried out every four months for the first two years, every six months during the third year, and yearly thereafter. History and physical, including thorough ENT examination, will be performed to assess the local-regional disease status and detect distant spread, In addition, treatment related complications will be graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme *(Appendix IV)*.

11.3 CBC, SMA-12 and chest x-rays will be performed every six months for two years and yearly thereafter. Other metastatic workup will be carried out as indicated from the findings of history and physical.

12.0 DATA COLLECTION *(4/29/94, 12/23/94)*

12.1 Summary of Data Submission

ECOG data *(including pathology materials)* will be sent to the appropriate ECOG Office according to the following schedule and then forwarded to RTOG Headquarters. All dosimetry material *(films, etc.)* must be identified with labels available from your Cooperative Group. **All data items must be identified with both RTOG's and ECOG's study and case numbers. Unidentified data/films will be returned.**

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Diagnostic Pathology Report **(P1)** Pathology Form **(P4)** Surgery Form **(S1)** Operative Report **(S2)** Surgical Pathology Report **(S5)**	Within 2 wks of study entry
Radiotherapy Form **(T1)** *(Arm 1)* Final Dosimetry Information: Dose Calculations **(TL)** Daily Treatment Record **(T5)** Isodose Distribution **(T6)** Polaroid of RT field **(T7)** Localization & Portal Films **(TP)**	Within 1 week of RT end
Follow-up Form **(F1)**	Every 4 months for the first two years; q 6 mos for the third year, then annually, at progression/relapse and at death.
Autopsy Report **(D3)**	As applicable

12.2 Data

The RTOG assigned case and study number must be recorded on all data items submitted. Data will be routed according to the mechanism set up by each participating Group. Generally the participating Group will require data to be routed through their offices and they will send the forms to:

American College of Radiology
Radiation Therapy Oncology Group -14th Floor
1101 Market Street
Philadelphia, PA 19107

12.2.1 *ECOG Institutions*

The required forms are attached to the protocol *(ECOG version)*. Additional forms will not be supplied when patients are randomized. It will be the responsibility of the participating institutions to copy the attached forms and to maintain a supply of available forms for data submission.

Originals of completed forms must be sent by the institution to the ECOG Statistical Center Data Management Office *(ATTN: DATA)*, 303 Boylston Street, Brookline, MA 02146. *(The RTOG accession number, as well as the ECOG sequence number, must appear on all forms)*.

ECOG institutions' final dosimetry information should be sent directly to RTOG.

12.3 Request for Study Information and Forms Request

Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Response should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically *(generally three times a year)* computer-generated lists identifying delinquent material are prepared and routed through the participating Cooperative Group for distribution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Overview

The primary objective of this study is to evaluate the effectiveness of post-operative hypofractionated radiotherapy in preventing loco-regional failure in patients with nodal metastases from cutaneous melanoma. The analysis of the MDACC experience with and without adjuvant radiation therapy showed that nearly all the local regional failures occurred in the first two years. For planning purposes, it will be assumed that all these failures will occur in the first two years in this protocol and for sample size estimation a binomial distribution will be used where failure is defined as local or regional recurrence within two years. In addition, the treatments will be also compared with respect to NED survival and overall survival. These two endpoints are considered as secondary endpoints. It is not anticipated that there will be a striking difference in the treatment arms with either of these endpoints.

13.2 Study Endpoints

13.2.1 Local-Regional Control Rate

13.2.2 NED Survival *(Failure: any disease progression -local, regional, distant - or death from any cause)*

13.2.3 Overall Survival *(Failure: death from any cause)*

13.2.4 Toxicity

13.3 Sample Size Estimation

As mentioned in Section 1.0, a retrospective review of patients without postoperative radiation therapy at MDACC reported an estimated Kaplan-Meier *(KM)* Two-year regional failure rate of 46%. The recent update *(6/93)* of the MDACC experience with postoperative radiation therapy found a KM estimate of 10% for the two year local/regional failure rate. Gelman et al.[10] and Gaynor et al.[11] pointed in their respective papers that the KM methods would tend to overestimate these local regional rates. In spite of this overestimation, the two historical series suggest that a difference of 20% is plausible to test for. Using 35% as the baseline failure rate, 134 evaluable patients will be needed for one sided test of the hypothesis with the significance level of .05 and with statistical power of .80. To guard against a potential 10% loss of patients due to ineligibility or due to no data submission, **the targeted sample size has been set at 148 patients**.

13.3 Patient Accrual

The projected accrual rate from RTOG institutions is three cases per month and thus, this study will take about 4 years to reach its accrual target. ECOG and the Sydney Melanoma Group have expressed interest in the study and, if they do join, it is anticipated that the accrual phase will shorten by a year. If the average monthly accrual rate is < 2 cases, the study will be re-evaluated with respect to inviting participation from other cooperative groups.

13.4 Randomization Schema

The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.[12] The stratifying variables include: extracapsular extension *(yes vs. no)*, prior systemic *(chemo- or biological)* therapy *(yes vs. no)*, and number of involved nodes *(1-3 vs. > 3)*

13.5 Analyses Plans *(revised 4/29/94)*

13.5.1 *Interim analysis*:

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery with the protocol distributions of important prognostic baseline variables and the frequencies and severity of the toxicities.

The first significance test comparing the local-regional failure rates between the two treatment arms will be performed for the first RTOG semi-annual meeting after 50% of the required sample size is available. The log rank test will be used to compare the two options because it allows censored observation before two years. The result will be then reported to RTOG Data Monitoring Committee *(DMC)*.

If the local-regional failure rate for postoperative RT arm shows a highly significant improvement *($p < .001$)* over the local-regional failure rate for the no RT arm , the study statistician will recommend to the DMC that the randomization be discontinued and study be immediately written up for publication.

The second significance test comparing the local-regional failure rates between the two treatment arms will be performed for the first RTOG semi-annual meeting after 100% of the required sample size is available and the result will be then reported to the DMC. The log rank will be used to compare the two options. If the local-regional failure rate for postoperative RT arm shows a highly significant improvement over the local-regional failure rate for the no RT arm *($p < .001$)*, the study statistician will recommend to the DMC that the study be written up immediately.

13.5.2 *Analysis for Reporting the Initial Treatment Results*:

This major analysis will occur after each patient has been potentially followed for a minimum of 24 months unless the study is stopped earlier. It will include a tabulation of all cases entered, those excluded from the analyses, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints described in section 13.2. The significance level of 0.048 will be used in this analysis to preserve an overall significance level of .05 for the study.

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APPENDIX I

RTOG 93-02
ECOG R9302

A PROSPECTIVE RANDOMIZED PHASE III CLINICAL TRIAL EVALUATING THE USE OF POST-OPERATIVE ADJUVANT RADIOTHERAPY IN THE TREATMENT OF PATIENTS WITH CUTANEOUS MELANOMA OF THE HEAD AND NECK

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have a melanoma of my head and neck region which has spread to my lymph node(s). My doctor feels that my participation in this study may be helpful. This is a clinical research study to determine if the use of radiation after the wound has healed will decrease the incidence of disease recurrence and to determine the degree of side effects from the use of radiation following surgery.

DESCRIPTION OF PROCEDURES

The therapy which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two selections by computer. The chance of my receiving either is approximately equal. I will be assigned to either five treatments of radiation or observation only. If I am assigned to radiation, it will be given twice a week for approximately 2 1/2 weeks and will include the primary node *(gland)* site as well as one side of the neck and/or parotid gland area.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks of Radiation: Temporary loss of hair or reddening or tanning of the skin in the area of radiation, mild soreness in the mouth and throat, reduction of salivary flow and dental cavities. My teeth will be evaluated by my dentist and any which are unrestorable and in the field of radiation will be removed. Any damage to the teeth or jaw bone is minimized with the use of fluoride.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests and chest X-ray will be done twice a year to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment for injury will be available. I understand, however, I will not be provided with reimbursement for medical care nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr._____ the investigator in charge, at_____. In addition, I may contact _____ _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include surgery alone, immunotherapy, or chemotherapy which may make me feel better, but not necessarily cure me or make my disease less. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs and some of these costs may not be covered by insurance.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature (or Legal Representative) Date

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 processes progressing rapidly
0	Dead,

APPENDIX III

AJCC STAGING SYSTEM FOR MALIGNANT MELANOMA (1983)

STAGE I

Localized melanoma ≤ 1.5 mm

A. ≤ 0.75 mm or Level II *(T1 N0 M0)*

B. 0.76 -1.5 mm or Level III *(T2 N0 M0)*

STAGE II

Localized melanoma > 1.5 mm.

A. > 1.5 to 4 mm or Level IV *(T3 N0 M0)*

B. > 4 mm or Level V *(T4 N0 M0)*

STAGE III

Limited Nodal Metastasis *(1 nodal basin)*
or < 5 In-Transit Mets

STAGE IV

Advanced Regional or Distant Metastasis

APPENDIX V *(revised 4/29/94)*
ADVERSE REACTION REPORTING GUIDELINES

A. General Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires special handling, study specific reporting procedures supercede the general guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff *(215/574-3214)*. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction. ECOG Institutions will report details to ECOG Data Management (617) 632-3610.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .

3. A written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol. *(FAX #215/928-0153)*. ECOG Institutions will send written reports to ECOG Data Management, ATTN: ADR.

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group *(in the case of RTOG-coordinated intergroup studies)* must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG coordinated Intergroup studies is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. Radiation Toxicity Guidelines

1. All fatal toxicities *(grade 5)* resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening *(grade 4)* toxicities from protocol therapy must be reported by telephone to the Group Chairman, RTOG Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

APPENDIX VI

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

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 carries.
3. To allow proper fitting of dentures following treatment.

PREIRRADIATION CARE AND PROCEDURES

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature us 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.

Group 3

Includes those in who 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 1/2 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 restorations of the remaining teeth as required. The patients are instructed for dental prophlayxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom 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 carriers.

EXTRACTION OF TEETH

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that primary closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

CAUSATIVE FACTORS

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduction of pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed and those teeth with large amount of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

PREVENTIVE PROGRAM

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply houses. This material is 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 the 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 the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries 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 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 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 to 10 to 15 minutes 3 times a day is recommended.

INFECTIONS

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

BONE NECROSIS

The patients receiving radiation therapy of 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 severely limited repair process. Bone necrosis occurs most often after post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX VIII *(added 4/29/94)*

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

I. REGISTRATION: RTOG will be responsible for all registration/ randomizations. The procedure is:
-Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
-The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
-RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forward a copy of the calendar to the participating institution.

II. PROTOCOL DISTRIBUTION: Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.

III. INSTITUTIONAL PARTICIPATION: It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.

IV. CONFIRMATION/CALENDARS: A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code which appears on the Calendars in the "key" columns is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items which are not forms (CAT Scan reports, pathology reports) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

V. FORMS: Forms packages may be obtained from the participating Cooperative Group office. Attached is a list (Forms Package Index) of all data collection forms used in the study, the toxicity criteria for this study, if applicable and a sample of the data collection forms.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (see below), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to

American College of Radiology
Radiation Therapy Oncology Group - 14th Floor
1101 Market Street
Philadelphia, PA 19107

VI. LABELS: Preprinted labels are available for source document data items (radiographic reports, etc.) Supplied white labels are to be used for film identification.

The blank labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Data managers are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be cancelled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission.

VI. RAPID REVIEW ITEMS: Time critical data which requires rapid submission must be sent directly to RTOG (See Section V). These items are:

M2 - Medical Oncology Treatment Planning Form (if required by the Protocol)
T2 - Protocol Treatment Form
T3 - Photon Localization film (for all fields treated initially)
T4 - Photon dose calculations (for all fields treated initially)

IX. REQUEST FOR STUDY INFORMATION AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (generally three times per year) computer generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

Randomization/Registration	Registration Secretary (215) 574-3191
Pathology	Pathology Clerk (215) 574-3161
Protocols/Amendments	Protocol Administrator (215) 574-3195
Data/Eligibility/Treatment/ Adverse Reactions/Data Management Procedures	Data Manager (215)574-3214
Radiotherapy data items (films, radiographs, isodose summations, treatment records, scans, reports and calculations)	Dosimetry Clerk (215) 574-3219

XI. ADVERSE REACTIONS/AND TOXICITY

From Radiotherapy: Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters, the Group Chairman Dr. James Cox and to the Study Chairman. If the Chairman is unavailable, ask to speak to the Data Manager for this study. ECOG Institutions: report details to the ECOG Data Management Office 617/632-3610. Send written reports to the ECOG Data Management Office, ATTN: ADR.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters and the Study Chairman are to receive notification as outlined by the NCI procedures, i.e. if telephone notification is necessary, RTOG and the Study Chairman must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.