RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITA

RTOG Study Chairs (Continued) [3/4/10]

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This study is supported by the NCI Cancer Trials Support Unit (CTSU). [9/22/09]

RTOG Institution # __________

RTOG 0617 **<u>ELIGIBILITY CHECKLIST</u> (3/4/10)**

Case # _________ (page 1 of 3)

___________(Y) 1. Does the patient have histologically or cytologically documented NSCLC within 12 weeks of registration? (patients who present with N2 or N3 disease and an undetectable NSCLC primary tumor also are eligible.)

___________(N) 2. Has the tumor been totally resected?

__________ (Y/NA) Has the patient had a nodal recurrence after surgery for an early-stage NSCLC and have the criteria in Section 3.1.2 been met?

___________(Y) 3. Is the patient IIIA/ IIIB with no evidence of distant metastasis (M0)?

___________(N) 4. Does the patient have supraclavicular or contralateral hilar disease? (The presence of supraclavicular or contralateral hilar disease would make the patient ineligible).

___________(Y) 5. Is the patient's Zubrod Performance Status 0-1?

___________(Y) 6. Were all pre-registration labs done within the specified timeframes and are the patient's lab values within the parameters of eligibility in Sections 3.1 and 4.1?

___________(Y) 7. Is the FEV1 best value ≥≥4 590% predicted)58)203.6(Iere all phe Frequie4-dpre-0.0028 Tetion NSCLC 69TJ207.8

RTOG Institution # _____

RTOG 0617 **ELIGIBILITY CHECKLIST (9/22/09)**

RTOG Institution # _____

RTOG 0617 **ELIGIBILITY CHECKLIST (9/22/09)**

Case # _____ (page 3 of 3)

_____ 18. Medical oncologist

_____(Y/N) 19. Tissue kept for cancer research?

_____(Y/N) 20. Urine kept for cancer research?

_____(Y/N) 21. Blood kept for cancer research?

_____(Y/N) 22. Tissue kept for medical research?

_____(Y/N) 23. Urine kept for medical research?

_____(Y/N) 24. Blood kept for medical research?

(Y/N) 25. Allow contact for future research?

26. Specify Radiation Technique (3D-CRT vs. IMRT)

27. Specify Zubrod Performance Score (0 vs. 1)

(Y/N) 28. PET staging?

_____ 29. Specify histology (squamous vs. non-squamous)

_____(Y) 30. I attest that I am willing to treat this

_____Y/N) 31. Did the patient agree to participate in the Quality of Life component of the study?

_____ If no, please specify the reason from the following:

1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

The Eligibility Checklist must be completed y prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1 Disease Background

Lung cancer remains the leading cause of cancer death in the United States, a

These three phase III trials consistently demonstrated longer survival for the concurrent arms, and this difference was significant in two of the three trials. Based on these results, concurrent chemoradiation has become the standard of care since 2001. It is important to note that toxicity is significantly greater with concurrent chemotherapy.

Tf.2 Rationale for Carboplatin and Paclitaxel

geometry and weighting through the forward planning process. The importance of improved target delineation cannot be overemphasized. Once patients are immobilized and CT-scanned in the treatment position, the radiation oncologist can delineate the tumor and adjacent tissues in three dimensions, choosd509 amandgls Omaximzedtumor acvereage,and /r aminimzedt]TJ-21.69 aModernTreatment pomning psystems enabl the tfu]TJ2

NSCLC.

Esophageal injury can be reduced by limiting the volume of esophagus in the radiation field or the mean esophageal dose.[58]

Table 3: Esophageal injury after high-dose radiation therapy for NSCLC

Author (# patients)	Incidence grade ≥3		Predictive factors
	Acute	**Late**	
Singh[59]	5% 6%	Max/mean dose, for	chemo/radiation therapy
Rosenman[11]	8% 6%	Length 40-60 Gy	
Maguire[60]	11%	3%	Chemotherapy, L_{50}, V_{50},

produce both TGFα and EGF.[67] An antagonist directed against the ligand-binding site of EGFR offers an interesting approach to the therapy of cancers involving unregulated EGFR-dependent pathways. Among those cancers that overexpress EGFR are some of the most prevalent, including: esophageal 92%, head and neck 90%, colorectal 72%, prostate 65%, bladder 65%, ovarian 60%, cervical 60%, pancreatic 89%, renal cell 50%, and lung 50%.[68-70] Prognosis for many of these malignancies is poor if not diagnosed at an early stage, and therapy for advanced

volume of distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented below:

Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Cetuximab plus Radiation

Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma

[3] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticar0.00

therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with

Comparison of Grade >3 Non-Hematologic Events Between Two RTOG Studies

Grade 3-5 non-hematologic toxicities	**ACR 427**		**RTOG 0324**	
	No.of pts	**(%)**	**No.of pts**	**(%)**
Cardiac	7	8	4	4
Gastrointestinal	32	35	14	15
Pulmonary/upper respiratory	15	16	17	18
Neurology	10	11	8	8.6
Total Adverse Event Rate (All Events)	60%		63% e	

4.2.6 Specimens for Translational Research

5.2.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

5.2.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See

For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged.

For institutions with gating technology, the use of respiratory gating is encouraged.

There are 2 components to the PTV expansion. the internal motion (IM margin) which should be at least 1 cm in the inferior-superior direction, and 0.5 cm in the axial plane and an additional set-up margin (SU margin) of 0.5 cm. Thus, the total PTV includes the CTV plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord, or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited to 0.5 cm towards this particular dimension (skin or spinal canal).

6.4.1.4 Normal anatomy to be identified: The normal anatomy to be outlined on each CT image will

the situation. The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient.

6.5.5 Heart: The following limits are recommended: 60Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart.

6.6 Documentation Requirements

6.6.1 Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter

Concurrent Cetuximab and Chemotherapy for Arms C & D: The patients randomized to

[redacted]

20.32

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentra

METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness;

7.8.4 Storage

Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.8.5 Adverse Events Unopene2880./08) Unopene2880./582419

Hematologic: Myelosuppression

Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia

Neurological: Peripheral neuropathy, ocular changes

Other: Ototoxicity, myalgia, fatigue, allergic reaction

7.8.6 Supply

Carboplatin is commercially available.

7.9 Dose Modifications (6/18/08)

7.9.1 Paclitaxel and carboplatin infusions will not be concurrently withheld if cetuximab is withheld. Likewise, if paclitaxel, carboplatin, or RT are delayed or withheld, cetuximab will not be concurrently delayed or withheld, unless required by parameters

infusion, at the end of the infusion and 1 hour post-infusion. For subsequent infusions, vital signs should be taken pre- and post-infusion.

7.9.3.1 *Treatment of Cetuximab Infusion Reactions*

Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both adverse events. Cytokine release syndrome/acute infusion reactions may occur with an agent that causes cytokine release, e.g., with a monoclonal antibody such as cetuximab. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms are similar to those of allergic reaction/hypersensitivity: arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, fever, headache, hypertension, hypotension, myalgia, nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating, tachycardia, tumor pain, urticaria, and vomiting.

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, co-0.0osteroids, intravenous antihistamines, bronchodilators, and oxygen

Worst Toxicity NCI CTCAE Grade (CTCAE v3.0) [a, d]	Paclitaxel Dose At Start of Subsequent Cycles of Therapy [b]	Carboplatin Dose At Start of Subsequent Cycles of Therapy [b]	Cetuximab Dose At Start of Subsequent Cycles of Therapy [b,c]

Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Courier Address (FedEx, UPS, etc.): <u>For Frozen Specimens</u>
RTOG Biospecimen Resource

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and other organ systems and that RNA expression and protein levels in WBC more closely reflect the effects of the chemoradiation therapy at cellular levels whereas DNA polymorphism reflects the inherited genetic background. 30 ml peripheral blood will be taken from each individual before treatment, 20 ml at four weeks after initiation of treatment and at the first follow up after complstion of concurrent chemoradiotherapy in order to determine baseline and short-term and long-term responses after concurrent chemoradiotherapy. 10-20 ml urine will also be collected in the morning of each day when blood is collected for potential biomarker related study.

Our current plan is to subject the samplss to DNA polymorphism analysis using restriction fragment length polymorphism-polymerase chain reaction, global gene expression profiling and cytokine microarray analysis (RayBio human cytokine array; RayBiotech) that measurss ar leve of 174 cytokines, and growth factors, implicated in human diseases. A newly available phosphor-protein antibody array (73 proteins) will also be used for WBC samplss. Although the assays are relative quantification, it is adequate for initial comparative analysis because we will be comparing two groups of patients and samplss from the same individuals before and after arany3 T000lw[(refparaents)3.970is adequate eand othe inta2 Tcor inzdiseawit will b

RTOG v3317.4(0617)]TJ/F1

c. Centrifuge within one hour of collection in a standard clinical centrifuge at 3000g at 4

10.5.5 Specimen Collection Summary **(10/29/10)**

Specimens for Tissue Banking/Central Review/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge. Pre-treatment, 4 weeks during treatment, and post-treatment at first followup.			

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names wity apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (10/9/08)

Item	Due

(RT) dose question [primary endpoint (1)] will

analysis, for each of the two questions, overall survival will be estimated by the Kaplan-Meier method.[111] The distribution of overall survival estimates between the control and experimental groups will be compared using the log rank test.[112] The same estimation method and statistical test will be used for progression-free survival. The cumulative incidence method will be used to estimate local-regional failure rates and the failure rates between the control and experimental groups will be compared using the failure-specific log-rank test.[113] Associations between time-to-event endpoints and covariates of interest that are of secondary interest will be investigated using the Cox proportional hazards model.

cetuximab arm. A negative interaction would compromise the ability of this trial to answer the cetuximab question. In order to address this concern, the completion of the cetuximab treatment course will be evaluated and reported using the following definition of completion:

- Patients must receive 70% of the total cetuximab dose that they are expected to receive, allowing for protocol specified dose modifications. If a patient has a protocol permitted dose modification (Section 7.9.2: -1 dose level = 200 mg/m^2
  mg/m
  will be calculated using the current dose level they should be receiving, which will be either 250, 200, or 150 mg/m^2.

13.6.2.2 *Deaths on All Arms*

All deaths reported as related to treatment will be reviewed by an independent reviewer, Dr.

Table 3: Outcome Possibilities and Corresponding Actions for Interim Analyses

Primary Endpoint (1) (RT dose question)	Primary Endpoint (2) (cetuximab question)	Action
Reject H_0	Reject H_0	Stop accrual (if applicable), conclude (1) the OS rate of high dose RT is higher than standard dose RT and (2) the OS rate with cetuximab is higher than without it.
Reject H_1		

futility boundary is crossed for only 1 of the primary hypotheses, then the primary hypothesis for the remaining treatment question will be tested using the log-rank statistic with a 1-sided significance level of 0.025. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as other possible modifying factors, such as age, gender, race, and other patient characteristics that are imbalanced between the treatment arms. If feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

each

13.6.6 Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic ns(grc)6Reoporsc rhe Janumary31,

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Quality-adjusted survival is

REFERENCES (6/18/08)

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93. Butt Z, et al. Quality of life in lung cancer: The validity and cross-cultural applicability of the Functional Assessment of Cancer Therapy-Lung Scale. *Hemat Oncol Cuin N Amer.* 19(2): 389-420, 2005.

94. Chang CH, et al. Real-time cuinical applicationof quality of life assessment in advanced lung cancer.

- For patients receiving cetuximab, evaluation of blood pressure and overall physical condition each time cetuximab is given: midway through receiving the cetuximab, at the completion of cetuximab, and after receiving cetuximab

When you are finished with radiation therapy, chemotherapy (and cetuximab if you receive it)…

- Physical examination
- Evaluation of your weight and ability to carry out daily activities
- Evaluation of any side effects you may be having
- Routine blood tests (about 1-3 teaspoons of blood will be taken from your vein)

At the end of all treatment…

- Physical examination
- Evaluation of your weight and ability to carry out daily activities
- Evaluation of any side effects you may be having
- Routine blood tests (about 1-3 teaspoons of blood will be taken from your vein)
- Studies of your lung function
- An EKG, a test of your heart function
- CT scan of the chest and upper abdomen

You will need these tests and procedures in follow-up visits. They are being done to see how you and your cancer were affected by the treatment you received.

- You will be seen by your doctor every 3 months for the first year, every 4 months for year 2, every 6 months for years 3-5, then once a year for your lifetime
- You will have a CT scan or MRI of the chest and upper abdomen every 6 months for 2 years then once a year
- You will have studies of your lung function at 6 months from the end of all treatment and at 1 year

(3/9/09) You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have a 25%chance of being placed in one of four groups.

If you are in group 1 (called "Arm A"):

You will receive the standard or usual dose of radiation therapy. You will receive radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carbn2The

If you are in group 3 (called "Arm C"):
You will receive the standard or usual dose of radiation therapy. You will receive radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 8, 15, 22, 29, 36, and 43 during radiation therapy. You also will receive cetuximab on these days. After completion of the radiation, chemotherapy, and cetuximab, you will receive two additional cycles of

Less Likely

- Narrowing of the esophagus causing difficulty swallowing meals (requiring internal dilation or a feeding tube)
-

Risks Associated with Cetuximab (6/9/10)

Likely

-

•

What are the costs of taking part in this study? (6/18/08)

You and/or your health plan/ insurance company will need to pay for some or all of the costs of
alth plans will not pay these costs for people taking
ck with

_____. You can print a copy of the "Cli

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they

APPENDIX IV

APPENDIX V (10/29/10)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood

Kit contents:

One Red Top tube for serum (A)
One Purple Top EDTA tube for plasma (B)
One Purple Top EDTA tube for Whole Blood (C)
Twenty five (25) 1 ml cryovials
Styrofoam container (inner)

APPENDIX VI (10/29/10)

APPENDIX VII

Protocol treatment must begin within 4 weeks after patient registration to the trial.

DATA SUBMISSION AND RECONCILIATION (9/22/09)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB)