For Amendment 4 to: RTOG 0915, A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer

NCI/Local Protocol #: RTOG-0915/RTOG 0915

NCI Protocol Version Date: March 6, 2014

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.</td>
</tr>
</tbody>
</table>
| Title pages | • On the 1st and 2nd title pages, as required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.  
• On the 2nd title page, this amendment and the study closure date were added to the Document History table. |
| Schema page | As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”. |
| 6.4.2.1     | In item 3, a typographical error was corrected. |
| 6.10.1      | In the 2nd paragraph, the date and link for the NCI Guidelines was updated. |
| Informed Consent | No changes |
RTOG 0915, “A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer”

Principal Investigator: Gregory Videtic, 216-444-9797, videtig@ccf.org

RTOG 0915 has been updated as follows:

1st title page: “Study Chairs” was updated to the current RTOG standard text, “Study Team”, and the Senior Statistician was updated. In addition, the Activation, Closure, Version, and Update Dates were deleted to update the protocol to current RTOG standard of providing all protocol activity in a Document History table.

A 2nd title page was created in order to add a Document History table, and the version date of the protocol was bolded in the table to update the protocol to current RTOG standards. In addition, this update was included in the table.

Section 5.1.1: The link to the CTSU IRB/REB Certification Form was updated.

Section 6.4.2.1:
- In item 5b, “Volume”, the 1st sentence was corrected.
- In the heading of the 4th column of Table 1, “Gy” was corrected to “%”.
- In the last 2 rows of the 4th column of Table 1, the greater than symbol (>) was corrected to the less than symbol (<).

Section 6.5.1: In the heading of the table for “Arm 2”, the parenthetical phrase was corrected from “12 x 4 Gy” to “4 x 12 Gy”.

Section 6.10:
- In the 4th paragraph, the phrase, “including a male patient’s impregnation of his partner”, was added to the last sentence to update the protocol to current RTOG text.
- In the 2nd paragraph of “AdEERS Reporting Requirements”, the link to CTCAE, v. 4 was updated.
- The table under “Adverse Events and Serious Adverse Events” was updated to the current NCI standard.

Section 6.10.2 was updated to current RTOG standard text.

Section 10.4: The shipping and postal addresses for the RTOG Biospecimen Resource were updated. This change also was made in Appendix V.

Section 10.5: The link to the Reimbursement and Case Credit Schedule was updated.

Section 10.6: The link to the Patient Tissue Consent Frequently Asked Questions was updated.

Appendix I:
- Under “About Using Tissue and Blood for Research”, the link to the information sheet was updated.
- Under “Where can I get more information”, the TTY number was deleted as requested by CTEP.
RTOG 0915 has been amended as follows:

In a review of the manuscript describing the conduct of RTOG 0236 (SBRT in medically inoperable lung cancer) by the Journal of the American Medical Association (JAMA), the editors correctly pointed out that unconventional definitions of local control were used, which described only recurrence of the primary treated tumor. The editors indicated that failure within the involved lobe (part of the T-stage for lung cancer in the TNM system) should be considered a component of local control. The editors indicated that recurrence definitions should reflect upon the site's TNM staging. As such, a recurrence of the original primary tumor (originally characterized by the T of the TNM staging) is deemed a local recurrence. A recurrence in the primary tumor's draining lymph nodes (hilar and mediastinal as originally characterized by the N of the TNM staging) is deemed a regional recurrence. Finally, a recurrence in distant sites (originally characterized by the M of the TNM staging) is deemed a disseminated recurrence. Fortunately, in 0236, the specific patterns of recurrence within the lungs were collected, and the oversight was corrected. In a re-analysis of 0236, 3 additional patients had new nodules within the same lobe and were included in the local recurrence definition. The primary endpoint was more correctly stated as "primary tumor control" (not local control), this nomenclature was corrected throughout the 0236 manuscript, and actuarial data on local control defined as primary tumor control plus control within the same (involved) lobe as well as local-regional control was added.

RTOG 0915 used the same unconventional recurrence definitions as RTOG 0236. Therefore, the protocol has been amended and patterns of recurrence have been reclassified appropriately. The terms "local control" and "local failure" as related to study procedures (not introduction) have been changed to "primary tumor control" and "primary tumor failure" throughout the protocol. The following sections were amended for this change: Sections 1.2.1, 1.2.4, 1.3.1, 1.3.2, 2.2, 11.2.1, 11.2.3 (both tables were revised), 13.2, 13.6.1, 13.6.2.1, 13.6.2.4, 13.6.2.4.1, and 13.6.2.4.2.

Other Changes

Section 3.1.3.3: The chest x-ray required within 4 weeks prior to registration was deleted as the CT scan (or PET/CT) and a whole body FDG-PET required prior to registration are standard of care and are sufficient. Subsequent sections were renumbered appropriately.
The corresponding question, #7, on page 1 of the Eligibility Checklist also was deleted, and the pre-treatment chest x-ray also was deleted from Appendices I and II.

Section 5.1.2 was deleted as these requirements only pertain to studies involving drug treatment. The subsequent section was appropriately renumbered.

Section 6.5.2.11 was added to specify how to contour the great vessels. The subsequent section was appropriately renumbered.

Section 10.2.2: The phrase, "skin punch" was amended to "punch tool" to update the protocol to the current Biospecimen Resource standard text.

Section 10.3.6 was added to amend the protocol to current RTOG standard text, and the subsequent section was appropriately renumbered.

Section 10.5 was amended to the current RTOG standard text.

Appendix I: Under "You will need these tests and procedures in follow-up visits" and "Every 3 months in years 1-2, every 6 months in years 3-4 and then once a year", the description of the timeframe for chest x-rays and CT scans was corrected to be consistent with Section 11.1.2 and Appendix II.

Appendix II: Under the column for long-term follow up, an asterisk (*) was added for "chest x-ray" to refer sites to Section 11.1.2 for details concerning the timeframe for imaging.
RTOG 0915, "A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer"

**Study Chair:** Gregory Videtic, 216-444-9797, videtig@ccf.org

As mandated by CTEP, RTOG 0915 has been amended to require the use of CTCAE, version 4 for grading of all adverse events as of October 1, 2010.

The following sections were amended for this change: Sections 6.9.1, 6.9.3, in the 1st and 3rd paragraphs; Section 6.10.1, under "AdEERS Reporting Requirements" and "RTOG Reporting Requirements; Section 13.1, and Section 13.6.1
SUMMARY OF CHANGES
Amendment 1, Version Date: March 4, 2010
(Broadcast 3/16/10)

RTOG 0915, "A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer"

Study Chair: Gregory Videtic, 216-444-9797, videtig@ccf.org

RTOG 0915 has been amended as follows:

Eligibility Checklist, page 3: Questions 18-22 concerning specimens kept for research were reformatted to current RTOG standard.

Section 5.1.1: The 2nd bulleted item was amended to current RTOG standard.

Section 5.2.2.3: The e-mail address for ITC was updated. This change also was made in Sections 12.2 and 12.2.1.

Section 6.4.1: The 1st paragraph was amended to provide more details regarding the use of intravenous contrast during the planning CT. In addition, the 3rd paragraph was added to describe the acceptable methods to define the PTV, depending on the method of CT simulation. The final paragraph of the section was deleted, as it was redundant with the information added in the 3rd paragraph.

Section 6.5.1: The phrase, "Except for the rib" was added to the beginning of the 2nd sentence. In the tables for Arms 1 and 2, two asterisks (**) were added next to "Rib", and a note was added below the table regarding the rib limit. In addition, Section 6.5.1.1 was added to provide instructions to institutions regarding the rib and chest wall as critical structures.

Appendix I: Under "Where can I get more information?", the URL for the NCI general information web site was updated.
SUMMARY OF CHANGES
Update: September 3, 2009
(Broadcast: 9/3/09)

RTOG 0915 (NCCTG N0927), "A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer"

Study Chair: Gregory Videtic, MD; 216-444-9797; videtig@ccf.org

RTOG 0915 (NCCTG N0927) has been updated as follows:

Title page: NCCTG's designation for the trial, N0927, was added below the RTOG study number. This addition also was made on the Schema page and on the 1st page of Appendix I, the sample consent.

The demographic portion of the Eligibility Checklist was updated for database purposes as follows. No changes were made to the study eligibility criteria.

- Page 2, Question 14 was revised to the current RTOG standard text, "Method of Payment".
- Page 3, Question 18, "Medical Oncologist", was deleted, as it is unnecessary for this study. Subsequent questions were appropriately renumbered.

Section 6.10.1, under "RTOG Reporting Requirements": The MedDRA version was corrected from 9.0 to 10.0 to be consistent with the text in this section and with Section 6.9.1.

Section 10.5 was updated to current RTOG standard text.

Appendix VI, "Instructions for NCCTG Institutions", was added and the Index page was updated with this appendix.