For **Protocol** Amendment 6 to: RTOG 0920, A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer

NCI/Local Protocol #: RTOG-0920/RTOG 0920

NCI Protocol Version Date: January 23, 2013

Section	Change
Global	To comply with CTEP's new formatting/document requirements, the protocol was reformatted, and the sample consent was removed from the appendices (the subsequent appendices were appropriately renumbered); no substantive changes were made to the consent. The informed consent, formatted to CTEP's requirements, continues to be available in MS Word on the protocol page of the RTOG web site.
2nd Title page	The "Version Date" was deleted to update the protocol to the RTOG standard of bolding the version date in the document history table.
3rd Title page	This amendment was added to the document history table.
Index page	The Index was deleted and replaced with a Table of Contents, as required by CTEP's new document requirements.
Eligibility Checklist, Step 1	In question 16 on page 2, the phrase, "and/or pathology", was added after "operative" to be consistent with changes made in Section 3.2.
1.8	In Section 1.8.3, the timeframe for the assessments was corrected from "the start of radiation" to "the end of radiation".
3.2.2	The phrase, "and/or pathology", was added after "operative" for clarity. A reference to Section 8.1 was added parenthetically for clarity.
5.1	A heading was added, so this section could be listed in the required Table of Contents.
7.2	The 2nd sentence was added to the 1st paragraph to direct investigators to the black box warning for patients receiving radiation therapy in combination with cetuximab.
7.2.3	In the last sentence of this section, the 1-hour observation period after the cetuximab infusion was revised from "recommended" to "required".
7.2.4	As requested by CTEP, the CAEPR for cetuximab was deleted, as CTEP will no longer maintain or update the CAEPR. Three paragraphs were added under "Adverse Events".
7.3.5	In the 2nd table under "Cetuximab-related Rash", the 1st column was updated to CTCAE, v. 4.0 terminology. In addition, in the paragraph below the table, "Late Skin Changes", the 2nd sentence also was updated to CTCAE, v. 4.0 terminology.
7.5.1	The reference to the NCI Guidelines was updated.

Section	Change
8.1	A heading was added, so this section could be listed in the required Table of Contents. In the 1st paragraph, the 2nd and 3rd sentences were revised for clarity. In the 2nd paragraph, the 3rd bulleted item was added.
10.5	The heading was revised in order to list this section in the required Table of Contents.
11.6	In the 1st bulleted item, the reference to Section 6.7 was corrected to Section 6.9. The last bulleted item was revised for clarity.
13.0	The sections were renumbered to current RTOG standards and so that appropriate sections could be included in the required Table of Contents.
Appendix I (formerly Appendix II)	To comply with CTEP's new formatting requirements, the single table was reformatted to 3 tables: "Pre-Treatment Assessments", "Assessments During RT", and "Assessments in Follow Up". In Appendix I, "Assessments During RT", an asterisk (*) was added next to Na, K, Cl, glucose, Ca, Mg, albumin in the "Every 3 wks" row to refer investigators to Sections 11.1-11.3 for the instruction that these assessments are only for Arm 2 patients.

SUMMARY OF CHANGES
Update: June 14, 2012
(Broadcast 6/14/12)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 was updated as follows:

Second title page: In the sentences below the table, Dr. Cmelak was added as one of the ECOG Co-Chairs to be consistent with the first title page.

Third title page: This update was added to the "Document History" table.

Eligibility Checklist, Step 1, page 1: Question 11 was added to be consistent with Section 3.1.10, and subsequent questions were renumbered accordingly. No eligibility criteria were changed.

Section 5.5.2: In the 1st sentence, the phrase, "after pre-treatment evaluation", was changed to "evaluation for eligibility" to clarify that the evaluations in Section 4.0 (which do not affect eligibility) do not have to be completed prior to registration of the patient.

Section 7.5.2 was updated to current RTOG standard text.

Appendix I: The section, "Quality of Life Study", was updated with a question allowing the patient to consent to use the VisionTree Software to make the sample consent consistent with changes made in Amendment 4.

SUMMARY OF CHANGES
Update: April 5, 2012
(Broadcast: 4/5/12)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 was updated as follows:

First title page: Dr. Quon's contact information was updated.

The **second title page** was updated with ECOG's formal endorsement of the study. In addition, this update was added to the "Document History" table.

SUMMARY OF CHANGES
Update: February 23, 2012
(Broadcast: 2/23/12)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 was updated as follows:

One of the choices for the stratification variable, "Clinical Stage" (which was added in Amendment 5) was corrected from "T2-3" to "T1-3". This correction was made in the following sections:

- The **Schema**;
- **Eligibility Checklist**, Step 1, page 3, Question 27 (this change updated the *demographic* portion of the checklist; no eligibility criteria were changed);
- **Section 13.4**.

SUMMARY OF CHANGES
Update: February 13, 2012
(Broadcast: 2/13/12)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 was updated as follows:

Eligibility Checklist:

- Step 1, pages 2 and 3: Questions 3, 4, 7, 10, 12, 15, 17, 25, and 26 were updated to be Common Data Element (CDE) compliant.
- Step 1, page 3: Question 27 was added to ask sites to specify the patient's clinical stage; this question was added to be consistent with changes made in Amendment 5.
- Step 2, page 4: Questions 4, 6, and 8 were updated to be CDE compliant.

These changes update the *demographic* portion of the checklist; no eligibility criteria were changed.

Section 5.4.1: In the 5th paragraph, the phrase, "U.S. and Canadian", was updated to "ALL".

Sections 5.4.3, 5.4.4.2, and 7.2.7.1 were updated to reflect the current logistics for non-Canadian international institutions.

Sections 7.2.6 and 7.2.7: In the 1st paragraph, the phrase, "in the United States and Canada", was added for clarity.

Section 7.2.7: A header, "U.S. and Canadian Institutions", was added above the 2nd paragraph for clarity. In addition, at the end of the section in the street address for Biologics, "Westin" was corrected to "Weston".

Appendix I, under "Where can I get more information?": CTEP's TTY number was deleted to update the consent to CTEP's current standard text.

SUMMARY OF CHANGES
Amendment 5, Version Date: January 17, 2012

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 has been amended as follows:

Eligibility criteria have been amended to include patients with clinical stage T4a disease. As previously written, the only T4 patients allowed on this study were those with clinical stage T1-3 cancers who were incidentally found after surgery to have microscopic T4a disease. The study chairs have received innumerable queries from institutions regarding this criterion. Differentiating between a clinical stage T3 and T4 cancer depends heavily on the observer and subjective interpretation of radiological studies. Similarly, adjudicating whether a resected cancer is microscopic or gross T4 is extremely subjective. The standard of care for completely resected, margin negative T4a head and neck cancer is post-operative radiation therapy. There is no evidence that adding cisplatin or other chemotherapy adds benefit; it clearly adds toxicity. Thus, it is extremely important to test whether cetuximab can improve outcomes in T4 cases and including these patients will not significantly alter the scientific design or statistical considerations of this trial.

The following sections were amended for this change:

- **Schema page:** A stratification variable, "Clinical Stage" was added to the Schema and under "Patient Population", "T2-3" was amended to "T2-T4a";
- **Eligibility Checklist**, page 1: In question 3, "T2-3" was amended to "T2-T4a" and in Question 7, the word, "microscopic" was deleted in the 5th bulleted item;
- **Section 3.1.1**: "T2-3" was amended to "T2-T4a";
- **Section 3.1.3.5**: The 1st sentence was amended and the "note" was deleted.
- **Section 13.4** was amended to include the stratification variable, "clinical stage".

<u>Other Changes</u>

Title page: Dr. Nguyen-Tân was added as a Radiation Oncology Co-Chair. Dr. Quon's affiliation and contact information was updated. At ECOG's request, Dr. Cmelak was added as a Radiation Oncology Co-Chair.

Section 7.1.1: In the 2nd paragraph, the 2nd sentence recommending that cetuximab be administered prior to radiation therapy was deleted. Given that cetuximab has a long half-life, once the loading dose is given on week 1, the drug is systemically present at the time when radiotherapy begins. Hence, it is felt that the administration of the maintenance doses (weeks 2-7 that are given concurrently with radiotherapy) does not need to be restricted to prior to radiotherapy. This will enable greater flexibility for the treatment of patients on this trial. This change also was made in **Appendix I**, under "What will happen if I take part in this research study?": In the 3rd paragraph under "For Group 2 Patients", the phrase, "before radiation therapy", was deleted .

Section 11.2.2: The schedule of Na, K, Cl, glucose, Ca, Mg, and albumin testing was amended to include "every 3 weeks during radiation therapy".

Appendix II: The schedule of Na, K, Cl, glucose, Ca, Mg, and albumin testing was clarified, and a reference to Section 11.2.2 was added to direct sites to further details available there.

SUMMARY OF CHANGES
Update: November 15, 2011
(Broadcast: 11/15/11)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 has been updated for implementation of CTSU's Oncology Patient Enrollment Network (OPEN). The following changes were made:

- **Title pages**: CTSU's logistics and contact information were added in the 2nd text box on the 3rd page.
- **Index page**: Appendix VI, "CTSU Logistics", was deleted, and subsequent appendices were renumbered appropriately on the Index page, in **Sections 10.2, 10.4.1**, and in the **titles of the specific appendices**.
- **Eligibility Checklist**, pages 1 through 4: As required by NCI for Common Data Element (CDE) compliance, "RTOG" was deleted prior to "Institution #". In addition, on pages 2, 3, and 4, questions were updated to be CDE compliant.
- **Section 5.4**, "Regulatory Pre-Registration Requirements", was updated.
- **Section 5.4.1.1** was added.
- **Section 5.5.2**, was retitled, "OPEN Registration Instructions", and the section was updated.

Other Changes:
Section 10.5 and Appendices VI, VII, and VIII: The street address of the RTOG Biospecimen Resource was updated.

Appendix II: The CT with contrast, or CT/PET, and/or MRI of head and neck in follow up should be done as clinically indicated. The column under "Follow up" titled, "Both Arms: q3 mos. post-XRT, then q3 mos. x 2 yrs, q6 mos. x 3 yrs, then annually" was corrected to indicate this. **Appendix I**, under "You will need these tests and procedures in follow-up visits", was corrected to be consistent.

SUMMARY OF CHANGES
Amendment 4, Version Date: October 5, 2011

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 has been amended as follows:

Section 3.2.1: was amended to include patients with bilateral tonsil cancers, and patients with T1-2, N0, M0, resected differentiated thyroid carcinoma identified at the time of resection. Since the activation of this study, there have been a number of screened cases in which patients have had incidental differentiated thyroid cancers or bilateral tonsil cancer. The latter is almost certainly a manifestation of HPV-related carcinogenesis. These cases were deemed ineligible and were not enrolled; however, after discussion among the study chairs, it was felt that it would be highly unlikely that either of these diagnoses would impact on the patients' survival or on any of the trial's secondary endpoints.

Patients are offered the option of completing quality of life assessments online versus in hardcopy. The following sections were amended for this change:

- **Eligibility Checklist**—Step 2, page 4: Question 11 was added (and the subsequent question was appropriately renumbered).
- **Sections 1.8.4, 4.1.4.1, and 11.5.6** were added.
- **Section 12.1**: A "Note" was added next to the QOL forms informing sites that QOL forms completed online will be stored on the VisionTree web site and transferred to RTOG. In addition, "QOL Forms Cover Sheets" were added with a timeframe and instructions to sites.
- **References**: Three citations referenced in Section 1.8.4 were added.
- **Appendix I**:
  - Under "Will my medical information be kept private?", VisionTree Software, Inc. was added as an organization that may look at and/or copy patients' medical records.
  - Under "Quality of Life Study", the 4th paragraph was added describing the option of online completion of QOL forms.

<u>Other Changes</u>

Title page: In Dr. Machtay's affiliation, the name of the Cancer Center was updated from "Ireland" to "Seidman". In addition, the Activation Date was deleted, as this information is provided in the Document History table; the Version Date remains for clarity.

The following changes were made to the **Eligibility Checklist**:

- Step 1, page 2: Question 21, referring to the high-risk study, RTOG 0619, was deleted, as 0619 is closed.
- Step 1, page 3: Question 26 was revised for clarity.
- Step 2, page 4: Question 12 was revised for clarity.

Section 3.2.8 was deleted as it referenced RTOG 0619 which is closed, and the reference to 0619 in **Section 8.1** was deleted as well.

Section 5.4.1: The link to the Certification Form was updated, and the section was updated to current RTOG standard text.

Section 5.4.3.1: The link to instructions for international institutions was updated.

Continued on next page

Section 5.4.4.1: The location of the SASF on the RTOG web site was updated. This change also was made in **Section 7.2.7**.

Section 5.4.4.2 was updated to current RTOG standard text.

Section 5.5.2: The link to the Password Authorization Form was updated.

Section 7.1.1: The 5th paragraph was added to clarify that sites should avoid interruption of cetuximab therapy during radiation therapy in case radiation treatment is delayed. Drug concentration should be maintained at steady-state for optimal biological effect.

Section 7.3.5: The 2nd and 3rd sentences were added to clarify that cetuximab doses missed due to reasons other than drug-related toxicity can be made up at the discretion of the investigator.

Section 7.5: In the 3rd paragraph, the link to Adverse Event Information on the RTOG web site was updated

Section 7.6: The text and table was updated as required by NCI.

Section 10.3: The phone number provided for RTOG Headquarters was corrected.

Section 10.4.1: A "note" was added above the 1st paragraph regarding the time point for collection of blood to be consistent with changes made in Section 10.4.3 and Appendix II.

Section 10.4.3:

- In the 3rd row of the table, an option was added for sites to provide tissue cores and slides rather than a tissue block.
- In the 4th-6th rows, the number of cryovials for serum, plasma, and DNA were amended to current RTOG Biospecimen Resource standards. Corresponding changes were made in **Appendix IX**.
- In the "note" below the table, the time point for collection of blood (for a CBC and for research) was amended from "week 1 of radiation therapy" to "prior to the start of treatment" for clarity. This clarification also was made in **Appendix II**, the study parameter table. It is likely that the serum and plasma samples submitted for research will be used in future exploratory analyses of potential biomarkers of response and/or toxicity. These analyses could be compromised if the patient has started radiation treatment and/or cetuximab, since these treatments could alter the patient's baseline levels of these potential biomarkers.

Section 10.6: The link to the Reimbursement and Case Credit Schedule was updated.

Section 10.7: The link to the Patient Tissue Consent FAQs was updated.

Section 11.5: The timeframe for quality of life assessments was corrected to "…at 3, 12, and 24 months from end of RT". This correction also was made in **Section 12.1**.

The following changes were made in **Appendix I**:

- Under "Quality of Life Study", the number of questionnaires completed by patients was corrected from 5 to 4 (the PSS-HN is completed by a research nurse or research associate, not by the patient).
- Under "About Using Tissue and Blood for Research": In the 3rd paragraph, the link to the NCI information sheet was updated.

SUMMARY OF CHANGES
Amendment 3, Version Date: December 6, 2010
(Broadcast: 12/23/10)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 has been amended as follows:

Throughout the protocol, "CTCAE, v. 4.0" was amended to "CTCAE, v. 4" to update the protocol to current RTOG standards.

The time point for baseline quality of life assessments was amended for consistency and clarity, as follows:

- **Section 4.1.4**: The phrase, "prior to the start of protocol treatment", was amended to "prior to the start of treatment".
- **Section 11.5**: The phrase, "prior to the start of treatment", was added prior to "(baseline)".
- **Appendix I**, under "Quality of Life Study": In the 3rd paragraph, the phrase, "At your first visit", was amended to "Before you begin treatment".
- **Appendix II,** under "Pre-Treatment": The phrase, "Baseline assessment", was amended to "Prior to Treatment (Baseline)".

In addition, the timeframe for quality of life assessments in follow up was amended to 3, 12, and 24 months from the end of treatment (versus from the start of treatment) in **Sections 11.5, 12.1, 13.1.3, and Appendix II.**

Other Changes

First title page: Dr. Chung's affiliation and contact information were updated.

Second title page:

- Dr. Zhang's e-mail address was updated.
- The "Document History" table was added to update the protocol to current RTOG standards.

Section 3.1.2.2: The laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) was amended from required to "recommended but not required", as these patients would have had this procedure performed as part of their preoperative workup and/or intraoperatively, so this requirement was duplicative. The following sections also were amended to be consistent with this change: **Eligibility Checklist**, page 1, question 5, **Section 11.1.3**, and **Appendix I**, under "Before you begin the study".

Sections 3.1.3.4, 3.1.3.5, and 3.2.2: Details and instructions were added for clarity.

Section 5.5.1.4: The phone number provided for RTOG Headquarters was incorrect, and 2 correct numbers were added. This correction also was made in **Section 10.2**.

Section 7.5.3: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS. In **Appendix VI**, CTSU logistics, under "Serious Adverse Event (AE) Reporting", item 4 was amended to be consistent with this change.

Section 8.1: The timeframe in the 1st sentence was corrected from "within 7 weeks of randomization" to "within 7 weeks of registration".

Section 10.0: REFERENCES to RTOG 0514 were deleted (as that study closed after meeting its objectives), as follows:

- Section 10.1: In the 2nd paragraph, the phrase, "through enrollment on RTOG 0514", was deleted.
- Section 10.4: The 2nd and 3rd paragraphs were deleted.
- Section 10.6: The paragraph referring to RTOG 0514 was replaced with the RTOG current standard language regarding reimbursement.

The following changes were made to **Section 10.0** to update the protocol to current RTOG Biospecimen Resource standard text:

- Section 10.4.1: In the 1st paragraph, the phrase, "time point of study", was added, and the phrases, "and time" and "for 3 days" were deleted.
- Under "Storage Conditions", the phrase, "frozen specimens" was added in the 1st sentence.
- Section 10.4.3: Under the columns, "Specimens taken from the patient" and "Submitted as", the rows for serum, plasma, and DNA were amended.

Sections 11.3.1 and 11.3.2 were combined as Section 11.3.1 (and the subsequent sections appropriately renumbered), and the text was amended to require a history and physical by <u>one</u> of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon at the specified time points in follow up and to recommend versus require the laryngopharyngoscopy. **Appendix I**, under "You will need these tests and procedures in follow-up visits" and **Appendix II**, under "Follow up" were amended to be consistent.

Appendix I, under "Reproductive risks": The 2nd sentence was amended to be consistent with Section 3.1.9 to reflect that there is only 1 pregnancy test (before beginning treatment).

Appendices VII and VIII were deleted and replaced with Appendices VII, VIII, and IX, which include the current RTOG Biospecimen Resource text. The **Index page** was amended to be consistent.

SUMMARY OF CHANGES
Amendment 2, Version Date: June 21, 2010
(Broadcast 7/9/10)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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In response to CTEP's request for a rapid protocol amendment, **RTOG 0920** has been amended as follows:

Section 7.2.4: CAEPR v. 1.0, March 9, 2005 was replaced with CAEPR v. 2.1, March 31, 2010. The new CAEPR utilizes CTCAE, v. 4.0 language, unless otherwise noted. Note: CTEP's specific detailed changes listed below compare the new revised CAEPR Version 1.0, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. Please note that version 2.0 was never released.

- This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious.
- Added New Risk:
  - Less Likely: Weight loss
  - Rare But Serious: Infections and infestations - Other (aseptic meningitis)
  - Reported on Cetuximab Trials But with the Relationship to Cetuximab Still Undetermined: Hemolysis; Chest pain - cardiac; Keratitis; Colitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Ileus; Rectal fistula; Cholecystitis; Hepatic failure; Serum amylase increased; Hyperkalemia; Generalized muscle weakness; Ataxia; Intracranial hemorrhage; Peripheral motor neuropathy; Adult respiratory distress syndrome; Atelectasis; Skin and subcutaneous tissue disorders - Other (skin fissures); Flushing
- Decrease in Risk Attribution:
  - Changed to Reported but Undetermined from Possible: Blurred vision; Photophobia; Platelet count decreased; Hypokalemia; Hyponatremia; Hypophosphatemia; Dizziness; Tremor
- Provided Further Clarification:
  - Cytokine release syndrome/acute infusion reaction *(CTCAE version 3.0 language)* is now reported as Infusion related reaction.
  - Allergic reaction/hypersensitivity (including drug fever) *(CTCAE version 3.0 language)* is now reported as Allergic reaction (Less Likely) and Anaphylaxis (Rare but Serious).
  - Voice changes *(CTCAE version 3.0 language)* is now reported as Hoarseness.
  - Footnote #2 was added to clarify those adverse events that were previously reported under Infection with Grade 3 or 4 neutrophils -

Secondary to dermatological toxicity and Infection with unknown ANC - Select *(CTCAE version 3.0 language)*.

- Mucositis/stomatitis (functional/symptomatic) - Select and Mucositis/stomatitis (clinical exam) - Select *(CTCAE version 3.0 language)* is now only reported as Mucositis oral.
- Cardiac arrhythmia *(verbatim from source documents)* is now reported as the following individual events: Atrial fibrillation, Atrial flutter, Paroxysmal atrial tachycardia, Sinus bradycardia, Sinus tachycardia, and Supraventricular tachycardia.

CTEP's specific changes to the CAEPR (Continued)

- Modified Agent Specific Adverse Events List (ASAEL) Reporting Requirements:
  - Added: Constipation; Dry mouth; Dyspepsia; Weight loss; Dehydration; Hypomagnesemia; Arthralgia; Back pain; Myalgia; Allergic rhinitis; Hoarseness; Alopecia; Photosensitivity; Thromboembolic event
- Deleted Risk:
  - Possible *(CTCAE version 3.0 language)*: Sweating (diaphoresis); Edema, larynx; Hypoxia
  - Reported on Cetuximab Trials But with the Relationship to Cetuximab Still Undetermined *verbatim from source documents)*: Enteritis; Intra-abdominal abscess; Salivary gland changes

Appendix I, "Risks Associated with Cetuximab": The previous risks were replaced with CTEP's Risk Profile, which is being provided for the first time for this agent. Per CTEP, the following specific changes were made to the risk profile:

Added New Risks:

- Less Likely: Weight loss
- Rare But Serious: Inflammation of the lining of the brain and spinal cord

SUMMARY OF CHANGES
Amendment 1, Version Date: June 4, 2010
(Broadcast 7/9/10)

RTOG 0920, "A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer"

Study Chair: Mitchell Machtay, MD; 216-844-2530; mitchell.machtay@uhhospitals.org

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RTOG 0920 has been amended as follows:

As mandated by CTEP, the CTCAE version referred to in the protocol was revised from "CTEP's Active Version CTCAE" to "CTCAE, v. 4.0". The following sections were revised for this change: **Eligibility Checklist**, page 2, question 19, and **Sections 1.8, 2.2,1, 3.2.5.8, 4.1.2, 6.9, 7.3.3, 7.3.4, 7.3.5.3, 7.5, 7.6, 13.1.2, and 13.2.5.**

Other Changes

Title page: Dr. Machtay's fax number was added. Dr. Richard Jordan was added as a Pathology Co-Chair.

Index page: Appendix VII and VIII were added.

Eligibility Checklist, Page 1, Question 7, fifth bulleted item: The word, "microscopic", was added prior to "T4a primary tumor" to be consistent with Section 3.1.3.5.

Section 1.7.2: The 4th paragraph was amended stating that HPV analysis will now be done via p16 immunohistochemistry and providing the rationale for use of this assay.

The assessments previously in Section 4.1.1 were moved to **Section 3.1.10** (and the subsequent sections were appropriately renumbered), as these assessments are required prior to registration for eligibility (to rule out the grade 3-4 electrolyte abnormalities specified in Section 3.2.5.8). In addition, the previously required assessment, HCO3, was deleted, as the study treatment is not expected to cause clinically relevant changes in this biochemical parameter. This parameter was not measured in RTOG 0522 trial, and this did not affect the safety conduct of the trial. Hence, it is felt that removal of the measurement of this biochemical parameter is safe and acceptable. The HCO3 assessment also was deleted in **Section 11.2.2** and in **Appendix II**.

Section 3.2.5.8: In the 4th bulleted item, the required parameter for potassium was corrected from 3-5 mmol/L to 3.5 mmol/L.

Section 5.0: A statement was added that IGRT is mandatory when using reduced margins; (otherwise, IGRT is optional). This statement also was added in **Section 6.0**.

Section 5.5.1.4: A phone number was added for physicians or institutions to call to request the patient's EGFR level and/or HPV status after the patient has completed study treatment. The phone number also was added in **Sections 10.2 and 10.3**.

Section 10.2: Text was added to provide instructions for institutions unable to submit a tissue block for the required EGFR analysis (and for patients with oropharyngeal carcinoma, the required HPV analysis). In addition, **Appendix VII** was added to provide the specimen plug kit instructions.

Section 10.3: The phrase, "by p16 immunohistochemistry", was added to the 1st and 2nd paragraphs to describe the assay used for HPV analysis.

Section 10.4: Instructions were added for submission of optional specimens in Sections 10.4.1 and 10.4.3 for institutions unable to open RTOG 0514 at the time of patient enrollment (and the subsequent sections were appropriately renumbered). In addition, **Appendix VIII** was added to provide the blood collection kit instructions.

Section 11.1.1: The phrase, "7 weeks of registration", was replaced with "7 weeks prior to registration" for clarity.

Section 12.1: The schedule for the Follow-up Form (F1) was revised from "start of treatment" to "completion of RT".

Section 12.2: The phrase, "as described in QA guidelines", following "Hard copy isodose distributions" was deleted as credentialing and treatment planning guidelines are included in the text of the protocol and/or the ATC/RPC web sites

Section 13.5.1: As recommended by the FDA, the timeframe of "from the date of study registration", was replaced with "from the date of treatment randomization".

The following changes were made in **Appendix I**:

- Under "During the study", the blood tests previously listed under "Weekly during radiation or radiation plus cetuximab", were moved to a new heading, "At week 1 during radiation or radiation plus cetuximab" to be consistent with Appendix II.
- Under "During the study", the imaging under "If your study doctor recommends" was clarified to "CT scan with contrast, or CT/PET scan, and/or MRI of your head and neck". This clarification also was made under "You will need these tests and procedures in follow-up visits" (the last bulleted item under "For All Patients: Every 3 months…").
- Under "You will need these tests and procedures in follow-up visits", the heading of the 3rd paragraph was corrected to "At 1 month after you finish radiation therapy (with or without cetuximab)".
- Under "You will need these tests and procedures in follow-up visits", the heading of the 4th paragraph was corrected to "Every 3 months from the end of radiation therapy".

- Under "How long will I be in the study?", in the 3rd paragraph, the phrase, "every 3 months from the start of treatment", was corrected to "every 3 months from the end of radiation therapy".
- Under "Risks Associated with Radiation to the Head and Neck", the last bulleted item under "Less Likely, But Serious" was deleted, as the risk of "permanent hair loss" is correctly listed under "Very Likely". In addition, the parenthetical phrase, "(face, chin, neck)" was added to the risk of "permanent hair loss" under "Very Likely".
- der "Quality of Life Study", the timeframe in the 3rd paragraph was corrected from "start of your treatment" to "end of your radiation therapy".

The following changes were made in **Appendix II**:

- Under "Pre-Treatment" and "Within 8 wks prior to registration", an asterisk (*) was added to the Pathology Assessment to refer sites to Section 11.1.1 for details.
- Under "Pre-Treatment", the timeframes for the following assessments were amended to be consistent with Sections 4.1. and 4.2:
    - CT with contrast, or CT/PET, and/or MRI of the H & N;
    - Assessment of swallowing function;
    - Eval for G-tube placement;
    - EKG.