

SUMMARY OF CHANGES
Amendment 5, Version Date: February 28, 2012
(Broadcast: March 8, 2012)

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (860) 545-2803; jcoen@harthosp.org

RTOG 0712 has been amended as follows:

Title Page: Contact information for the principal investigator, Dr. Coen, was updated; protocol document history table updated per amendment.

Section 3.1.1: Time frame for "...diagnosis of primary carcinoma of the bladder..." revised from "within 6 weeks of registration" to "within 8 weeks of registration". A corresponding change was made to question 1 on page 1 of the **Eligibility Checklist**.

Section 5.2.1: "U.S. and Canadian" replaced with "All" in the first sentence; **Section 5.2.2.1** was reformatted.

Sections 8.4 (next to last sentence) **and 11.3.3** (second paragraph, second sentence): Regarding the two negative re-evaluations: text added to clarify that the negative post-induction evaluation should count as the first of the two evaluations. **Appendix II** (Study Parameter Table) was updated to reflect these additions to the text.

Section 10.3.1 and Appendix VII: The street address for the RTOG Biospecimen Resource was updated.

Section 11.3.2: In the third sentence, "The following should be assessed" was deleted.

Appendix I (Sample Consent):

Will my medical information be kept private?

- Per NCI, the paragraph beginning "A description of this clinical trial will be available..." [new FDA language per 21 CFR 50.25(c)] and the "Note to Informed Consent Authors" were inserted to provide additional details to participants and the local institution.

Where can I get more information?

- The NCI's TTY number is no longer in service and was deleted.

SUMMARY OF CHANGES
Update: September 27, 2011
(Broadcast Date: September 27, 2011)

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 726-5866; jcoen@partners.org

RTOG 0712 has been updated as follows:

Title Page: Dr. Lautenschlaeger is Translational Research Co-Chair for this protocol; his contact information has been added to the title page.

Section 7.10.1: The typographical error in the table (the next to last row) was corrected from 1.0 – 1.9 to 1.0 – 1.3.

SUMMARY OF CHANGES
Amendment 4, Version Date: April 14, 2011
(Broadcast Date: April 28, 2011)

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 726-5866; jcoen@partners.org

RTOG 0712 has been amended as follows:

Global: All web links and related descriptions to sub-pages of the RTOG web site were updated.

Title Page: Dr. Hunt's e-mail address and the telephone number for RTOG Headquarters were updated; the "Document History" table was added according to the new RTOG title page format.

Index: The separate listings for Appendixes VIII and IX were removed and are included under the new title, "Appendix VII: Biospecimen Collection Instructions".

Schema: Updated the format to allow for an easier understanding of the flow of assessments. The timelines for assessments also were updated.

Section 1.2: The second paragraph regarding biomarker screening technologies was added.

Section 2.0

- **2.2.5:** "DNA content parameters" revised to "DNA content metabolomic, and proteomic parameters".
- **2.2.8:** Acute and late toxicities biomarkers secondary endpoint added.

Section 3.1.9: Added timing of assessment for clarity.

Section 4.0

- **4.1 and 4.2:** Added clarification for assessments in these sections to be administered at baseline prior to any protocol treatment.
- **4.1.2:** Replaced the requirement for chest x-ray with a chest CT.
- **4.1.3:** Added clarification for lab assessments to be obtained no more than 4 weeks prior to registration.
- **4.2.1:** Added a reference to Section 10.0 for details on submission requirements.

Section 5.0

- **5.1.1:** Revised to remove reference to 3D-CRT QA guidelines.
- **5.2.1:** Details regarding regulatory document translation added per current RTOG regulatory processes.
- **5.3:** The RTOG web support e-mail address in the next to last paragraph was updated.
- **5.4.1:** Removed the reference to "week 7" for the post-induction response evaluation as it now will be required 3-4 weeks following the completion of induction chemoradiotherapy.
- **5.4.5:** Near the end of the section, the reference to "week 17" for post-consolidation and radical cystectomy was deleted.

Section 6.0

- Updated the start of consolidation following the post-induction evaluation per the new guidelines detailed in the schema.

- **6.8:** In the first sentence, the parenthetical phrase, “both radiation and chemotherapy”, was added to clarify that treatment interruption refers to both radiation and chemotherapy.
- **6.10:** “Cystitis” was added to the genitourinary radiation adverse events; “colitis, mucous-like stools” was added to the gastrointestinal radiation adverse events.

Section 7.0

- At the beginning of the section, added sentence that treatment, ideally, should start on a Monday, as noted in Section 6.0.
- **7.1.9:** Updated the time frame for the post-induction evaluation per the new guidelines detailed in the schema.
- **7.1.9.2:** Updated the time frame for the radical cystectomy per the new guidelines detailed in the schema.
- **7.2.9:** Added details for post-consolidation evaluation for consistency with Section 7.1.9.
- **7.3.1:** Updated the time frame for the start of adjuvant per the new guidelines detailed in the schema.
- **7.9:** Removed “cisplatin” from the heading as the text applied to all induction and consolidation treatment. Added “dose” to all tables to clarify the dose adjustment.
- **7.9.1:** Deleted the statement that suggested that labs could be drawn at the end of the week prior as they are required to be drawn within 24 hours of treatment. Also, clarification was provided that the dose modification guidelines in this section applied to cisplatin, gemcitabine, and 5-FU. Lastly, a paragraph was added regarding hematologic toxicities for consistency with Section 6.8.
- **7.9.2:** “Cisplatin” added to the heading of this section, for clarity.
- **7.9.2.1:** Added note that the judgment of the physician is to be used when dose modifying due to out of range Serum Creatinine. Added clarification that if cisplatin is held, the subject should be re-evaluated on day 1 of each week to restart. Units for CrCl were added to the table.
- **7.9.2.2:** “Cisplatin” added to the heading of this section, for clarity.
- **7.9.2.3:** “Cisplatin” added to the heading of this section. In the ANC column of the table, changed 1.0 to 1.2 for consistency with Section 7.12.2.1. Also, added a \geq before grade 3 to clarify that cisplatin should be held for grade 4 and 5 also.
- **7.10.1:** Added clarification dose modifications for 5-FU for myelosuppression should be assessed weekly. A heading also was added to the table.
- **7.10.2:** Added clarification that 5-FU should be held for the entire 72h infusion. A heading was also added to the table.
- **7.11.1:** Removed paragraph beginning, “a complete blood count and serum creatinine...” to avoid repetition as the information is already included in Section 7.9.1 and relates to cisplatin, gemcitabine, and 5-FU.
- **7.12:** Added “paclitaxel” to the title as this section refers to paclitaxel also.
- **7.12.1:** Changed AGC to ANC to provide consistency throughout the protocol. Added instructions regarding holding or delaying of drug during adjuvant therapy. A table for dose modifications of cisplatin related to hematologic toxicities was added. The table for dose modifications of cisplatin related to nonhematologic toxicities was edited to provide more accurate instructions. The section also was rearranged to provide a clearer flow through dose modifications during adjuvant therapy.
- **7.12.2.1:** Added instructions regarding subsequent dose modifications after holding of day 8.
- **7.14:** In the first paragraph under “Adverse Events”, the sentence referencing the CTEP home page was deleted; the last sentence regarding study case report forms was added for clarity to institutions. Also, the paragraph immediately above Section 7.14.1 regarding AE notification to CTEP was added.
- **7.14.2:** In the next to last paragraph of the section, the reference to the NCI fax number was deleted.
- **7.14.3:** Updated per current AdEERS reporting requirements for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Section 8.0

- **8.2:** Removed the reference to week 7 for the post-induction response evaluation as it now will be required 3-4 weeks following the completion of induction chemoradiotherapy.
- **8.3:** Updated the time frame for the radical cystectomy per the new guidelines detailed in the schema.
- **8.4:** Updated the start of consolidation following the post-induction evaluation per the new guidelines detailed in the schema.

Section 10.0

- **10.2.2:** In the first sentence, “skin punch” replaced with “punch tool”.
- **10.2.5:** References to Appendixes VIII and IX were removed; the details from these appendixes now are included within Appendix VII. Also, “time point of study” was added to the list of information required for the Specimen Transmittal Form, and -20°C in the last sentence was replaced with -80°C .
- **10.2.6:** Added to provide details regarding frozen biospecimen storage conditions and shipping days.
- **10.3:** The specimen collection table was revised per the amended specimen collection procedures (additional specimen collection time points inserted).
- **10.3.1:** “U. S. Postal Service” added before the mailing address for non-frozen specimens.
- **10.4:** The RTOG reimbursement text was updated. The updated text includes a web address for the Reimbursement and Case Credit Schedule located on the RTOG web site.

Section 11

- **11.1:** Added, “See Sections 11.2 and 11.3 for details and/or exceptions to Appendix II.”
- **11.2.1 and 11.2.2:** In each section, the last sentence regarding plasma, serum, and urine collection was added.
- **11.2.1:** Added clarification that assessments should be done on day 1 of each week. Also, Zubrod performance status now will be required at day 1 of each week rather than the final day of treatment.
- **11.2.2:** Removed the reference to week 7 for the post-induction response evaluation as it now will be required 3-4 weeks following the completion of induction chemoradiotherapy.
- **11.2.3:** Removed this section and consolidated it with Section 11.2.4 (now 11.2.3). In the newly numbered Section 11.2.3, we added clarification that assessments should be done on day 1 of each week. Also, Zubrod performance status now will be required on day 1 of each week rather than the final day of treatment. Creatinine clearance also should be assessed weekly during consolidation. Added assessments to be done on day 1 of consolidation.
- **11.2.4:** Added this section to detail the assessments needed during the post-consolidation evaluation.
- **11.3.1:** Added clarification that these assessments are to be done prior to starting adjuvant treatment. Also clarified that a CT should be done both for abdominal/pelvic and chest, as well as a bone scan at this time point.
- **11.3.3:** Replaced the requirement for chest x-ray with a chest CT. Revised the requirement for radiographic evaluations to “every 6 months” rather than every 3 months in the first year and every 4 months in the second year. Also, a 10 year maximum for the required follow-up was provided. In addition, guidelines for the follow-up of patients who were discontinued due to progressive disease were added.
- **11.4.1:** Removed the reference to “week 7” for the post-induction response evaluation as it will now be required 3-4 weeks following the completion of induction chemoradiotherapy.
- **11.5:** Added the last bulleted item, “delay of more than 3 weeks due to an adverse event.”

Section 12

- **12.1:** Updated to correspond with assessment timing changes made within the protocol.
- **12.2:** The symbol (†) preceding “Digital Data Submission” under the “Preliminary Dosimetry Information” item list was deleted.

Section 13

- **13.1.2:** Added “metabolomic and proteomic” to the fifth bulleted item under “Secondary Endpoints”. This change is consistent with the change made in Section 2.2.5. The next to the last bulleted item, “To find potentially predictive biomarkers for acute and late toxicities”, was added; this addition is consistent with Section 2.2.8.
- **13.5.6:** In the second paragraph, “genomic, proteomic, or metabolomic” and “genomic, proteomic, and metabolomic” were added to the third and fourth sentences, respectively.

Appendix I (Sample Consent)

- The following sections of the sample consent were revised to correspond with changes made within the body of the protocol (assessments and timing):
 - What will happen if I take part in this research study/Before you begin the study

- During the study/Groups 1 and 2
- During the study/When you are finished receiving chemoradiotherapy (consolidation)...
- During the study/During additional chemotherapy
- During the study/ When you are finished with protocol treatment
- Study Plan/ If tumor has not completely disappeared
- How long will I be in the study
- Risks and side effects related to radiation therapy to the pelvis
- Under “About Using Tissue, Blood, and Urine for Research”, in the last sentence of the second paragraph, the NCI web site address was updated to the current web link. In the third paragraph, “before you start chemoradiation, three times during your treatment, at your 1-year follow-up visit, and in case your tumor comes back when this is detected” was revised to include the additional specimen collection times.
- Under “Making Your Choice”, the first and second questions about tissue, blood, and urine collection were revised per current RTOG format guidelines.

Appendix II (Study Parameters): Revised to correspond with changes made within the body of the protocol.

Appendix VII: Appendices VIII and IX were deleted from the protocol; the information included in these appendices now are detailed within Appendix VII under the title, “Biospecimen Collection Instructions”. Also, the appendices were revised according to the RTOG Biospecimen Resource procedures.

SUMMARY OF CHANGES
Amendment 3, Version Date: August 17, 2010
(Broadcast Date: April 28, 2011)

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 726-5866; jcoen@partners.org

RTOG 0712 has been amended as follows:

As mandated by CTEP, CTCAE version 3.0 reporting requirements were converted to CTCAE version 4.0.

- Changes were made to Section 7.14 of the protocol.

SUMMARY OF CHANGES
Amendment #2, Version Date: January 29, 2010
Broadcast: February 4, 2010

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 726-5866; jcoen@partners.org

RTOG 0712 has been amended as follows:

Section 6.5 (Critical Structures): The dose constraint for the femoral heads was revised from "Maximum dose to femoral heads less than 50Gy to a point that is at least 0.03 cc" to "No more than 20% of the volume above 50 Gy". This restriction is necessary to be able to consistently meet the more stringent rectal dose constraint.

SUMMARY OF CHANGES
Amendment #1, Version Date: January 21, 2010
Broadcast: February 4, 2010

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 726-5866; jcoen@partners.org

RTOG 0712 has been amended as follows:

Section 6.5 (Critical Structures): The rectal dose constraints were revised to lower the radiation DVH of the rectum while maintaining all of the required tumor doses.

Title Page: Dr. Coen's telephone number was updated (this change also was made in the "note" at the beginning of Section 6.0). The Senior Statistician is now Dr. Hunt.

Section 5.1.2: The web address for the ATC was updated.

Section 5.2.1: Updated per RTOG standard.

Section 5.3.1: The e-mail address for RTOG web support in the next to the last paragraph was updated.

Section 6.1.3: The section number for the reference to the criteria for dose coverage was revised.

Section 7.14.1: The web address for the NCI Guidelines on expedited adverse event reporting requirements was added.

Section 10.5: The web address for the RTOG Patient Tissue Consent Frequently Asked Questions sheet was updated.

Section 12.2: The web address for the Digital Data Submission Information (DDSI) Form and the e-mail address for the ITC were revised; the address for the DDSI form is case sensitive. Also, under the text about the DDSI form, "Hard copy isodose distributions for total dose plan (T6) as described in QA guidelines" was revised to "Hard copy isodose distributions for total dose plan (T6)" and "Available on the ATC website, <http://atc.wustl.edu/>" was deleted from immediately above "Note: All simulation and portal films and/or digital film images...".

Appendix III: Updated per RTOG standard.

Appendix VIII and Appendix IX: Updated per RTOG Biospecimen Resource standard.

SUMMARY OF CHANGES
Update: March 26, 2009
(Broadcast Date: March 26, 2009)

RTOG 0712, A Phase II Randomized Study For Patients With Muscle-Invasive Bladder Cancer Evaluating Transurethral Surgery And Concomitant Chemoradiation By Either BID Irradiation Plus 5-Fluorouracil And Cisplatin Or QD Irradiation Plus Gemcitabine Followed By Selective Bladder Preservation And Gemcitabine/Cisplatin Adjuvant Chemotherapy

Study Chair: John J. Coen, MD; (617) 724-1160; jcoen@partners.org

RTOG 0712 has been updated as follows:

Section 5.2: Regulatory requirements were updated to reflect current RTOG procedures.

Section 7.1.9.1: The consolidation therapy start time was corrected from 7-10 days to 7-14 days post induction response evaluation, to be consistent with the start date given for consolidation therapy in other sections of the protocol.

Section 7.3.1.2: Updated for clarity.

Section 7.12: The following was updated for clarity under "Dose Modification for Adjuvant Chemotherapy": (1) If creatinine clearance is below *60ml/min* prior to the start of a cycle, cisplatin should not be administered and the patient should receive paclitaxel as a substitute in all further cycles; (2) Patients should be given paclitaxel in place of cisplatin if creatinine clearance falls below 50ml/min. These updates were made because the accepted range for creatinine clearance is ≥ 60 ml/min.

Sections 8.2 and 8.4: Reference to "barbotage cytology" was replaced with "urine cytology" for consistency with Section 11.0 and Appendix II of the protocol.

Section 11.3.3: The third paragraph was updated to clarify that-as stated for pre-treatment assessment in Section 4.2-the urodynamic evaluation and AUA symptom score assessment are *recommended* evaluations in the third post-treatment year.

Appendix I (sample consent): To be consistent with the text in Section 4.2 and with the clarification made in Section 11.3.3 noted above, the bulleted text under "Before you begin the study" was updated to clarify that the AUA symptom score and urodynamic evaluation are recommended assessments. The bulleted text under "During the study/When you are finished chemoradiotherapy" was also updated. Also under "Before you begin the study", the text regarding the IVP, was deleted, as this assessment was removed from the protocol prior to activation.

Appendix VI: The cystoscopy report was replaced for readability.