Summary of Protocol Questions and Revisions

PRIOR TO PROTOCOL FINALIZATION 5/1/11

1) Would it not be "cleaner" just to include intact cervix patients on this study? If you end up with a small number of postop's they will be different than the mainly locally advanced group and may end up reducing the ability to show meaningful differences in Phase II. Do you think you will get enough in a randomized comparison to add data above that of the ~46 patients from RTOG 0418 that received IMRT for post-op cervix? The toxicity is different with conventional EBRT (with more small bowel and lymphedema in the post-op group). Obviously as well the intact cervix group gets a higher total dose with brachytherapy potentially to bladder and rectum. So there might be differing toxicity patterns seen. If the intact cervix cases make up say 90% of patients, retrospectively people may ask why post-ops were included. RTOG 0724 (that has only accrued 8/400 patients when I last checked) is in competition which may be cited by the funding body you are applying to.

IT WOULD BE CLEANER TO RESTRICT TO INTACT CERVIX PATIENTS, BUT RTOG 0418 WAS NON-RANDOMIZED AND HAS ONLY BEEN PUBLISHED IN ABSTRACT FORM, SO FURTHER STUDY OF IMRT IN POSTOP PATIENTS IS NEEDED. IN OUR PRIOR STUDIES, WE HAVE NOT OBSERVED A DIFFERENCE IN THE EFFECT OF IMRT ON ACUTE TOXICITY BASED ON POSTOP VERSUS INTACT STATUS. IF THERE IS NO DIFFERENCE IN EFFECT THEN IT WOULD MAKE SENSE TO INCLUDE BOTH POSTOP AND INTACT PATIENTS. POWERING THE STUDY TO TEST FOR AN INTERACTION WOULD REQUIRE MANY MORE PATIENTS. COMPETING TRIALS ARE ALWAYS A CONCERN, BUT THE GLOBAL SUPPLY OF CERVICAL CANCER PATIENTS IS ABUNDANT, AND MANY OF THE INSTITUTIONS PARTICIPATING IN THIS STUDY WILL NOT HAVE COMPETING STUDIES OPEN. ALSO, WE HAVE HAD PATIENTS ELIGIBLE FOR 0724 REFUSE BECAUSE OF THE ADDITIONAL CHEMOTHERAPY, BUT CONSENT FOR IMRT PROTOCOLS, SO IT MAY BE POSSIBLE TO ACCRUE TO BOTH RADIATION AND CHEMO STUDIES AT THE SAME CENTER, PARTICULARLY SOME OF THE HIGH-VOLUME CENTERS INVOLVED IN THIS TRIAL.

2) Should you specify the histologies permitted under invasive cervix cancer to exclude certain rare subtypes (clear cell, small cell neuroendocrine)?

THIS HAS BEEN CLARIFIED IN SECTIONS 2.0 AND 6.1.1 TO INCLUDE ONLY SQUAMOUS CELL CARCINOMA, ADENOCARCINOMA, OR ADENOSQUAMOUS CARCINOMA

3) We use 18MV for standard external beam (3D CRT) fields. The implication is that this would NOT be allowed for the conventional arm (it says 6-15MV)

18MV IS ALLOWED FOR CONVENTIONAL PLANS; SECTION 9.2.4.2 WAS MODIFIED

4) Should you define what involved pelvic nodal (unresected) metastases means? That is, if by CT or MRI what the criteria is if dissection is not done?
THIS HAS BEEN CLARIFIED IN SECTIONS 2.0 and 6.2.4 TO DEFINE GROSS PELVIC NODE METASTASIS AS EITHER BIOPSY-PROVEN AND UNDISSECTED (E.G. BY NEEDLE BIOPSY) OR PATHOLOGIC ON CT OR MRI (SHORT AXIS > 1 CM) OR ABNORMAL FDG UPTAKE ON PET OR PET/CT (AS DETERMINED BY RADIOLOGIST)

5) Should we limit total accrual from any one site?

WE DISCUSSED THIS WITH OUR STATISTICIANS, WHO ARE IN FAVOR OF A PER-INSTITUTION ACCRUAL LIMIT (SECTION 8.2.5). WE ARE PROPOSING AN ACCRUAL CAP OF 20 PATIENTS PER INSTITUTION FOR THE PHASE II PORTION OF THE STUDY AND 75 PATIENTS PER INSTITUTION FOR THE PHASE III PORTION, SO THAT NO MORE THAN ABOUT 20% OF THE SAMPLE IS REPRESENTED BY A SINGLE INSTITUTION.

6) For tomotherapy, oral contrast cannot be used unless simulations are performed on 2 different dates, as the tomotherapy planning system does not allow for contrast on the planning scan. Would you require 2 separate scans for tomo patients, or could the oral contrast be omitted?

SECTION 9.2.1.2 WAS MODIFIED TO MAKE ORAL CONTRAST OPTIONAL; PLEASE REVIEW CHANGES IN SIMULATION AND TREATMENT PLANNING PROCEDURES

7) Will staging the pelvic nodes with PET be acceptable? If positive on PET, then the nodes must be resected prior to chemoRT?

ABNORMAL FDG UPTAKE (AS DETERMINED BY RADIOLOGIST) IN A GROSS PELVIC NODE ON PET OR PET/CT IS AN EXCLUSION CRITERION. SECTIONS 2.0 AND 6.2.4 WERE REVISED TO CLARIFY THIS. STAGING BY PET IS ACCEPTABLE. IF THERE ARE GROSS PELVIC NODES THESE WOULD HAVE TO BE RESECTED TO BE ON THE PROTOCOL (OTHERWISE WE WOULD HAVE TO ALLOW FOR NODAL BOOST TECHNIQUES THAT WOULD COMPLICATE THE STUDY TOO MUCH)

8) It is occasionally necessary to take locally advanced cases to 50.4 Gy in order to facilitate brachytherapy placement. In such cases, would this be considered a protocol violation? Or would you prefer we stop at 45 Gy, even if it necessitates an interstitial implant?

THE NCIC AND RTOG TRIALS HAVE USED 45 GY FOR THE SAME POPULATION. I THINK WE SHOULD STANDARDIZE THE PELVIC DOSE SINCE THE DOSE IS SO CRITICAL TO THE EFFECT OF IMRT ON ACUTE TOXICITY

9) The rectal constraints will be difficult to meet, especially in intact cervix patients, in whom the rectum is often nearly entirely included in the PTV. I am currently working on a plan and ~95% of the rectum is included in the PTV. We probably won’t meet V45<50%--seems like rectum constraint shouldn’t lead to an ‘unacceptable’ deviation?

THE RECTAL CONSTRAINTS (SECTIONS 9.2.4.5 AND 9.2.4.6) WERE MODIFIED. V45 < 50% HAS BEEN MADE A SOFT CONSTRAINT (I.E., PLANNING GOAL /
GUIDELINE). MAX DOSE < 50 GY IS A HARD CONSTRAINT (I.E., FAILURE TO MEET RESULTS IN A PROTOCOL DEVIATION)

10) Will you capture information about the use of PM boost? It certainly will be indicated in some locally advanced cases. We often cover the PM with our interstitial brachy insertion, but I suspect many will use external beam.

WE ONLY PLANNED TO GATHER THE INFORMATION ON THE TREATMENT INFORMATION FORM (APPENDIX VI), AS TO WHETHER A PARAMETRICAL BOOST WAS GIVEN (YES/NO)

11) Daily CBCT can be used for daily set-up to bony anatomy, correct (just not for target volume IGRT)?

YES

12) Could you please clarify if microscopic intraperitoneal disease (for example, in the pelvis) is an exclusion?

PERITONEAL SPREAD MAKES THE PATIENT M1 (STAGE IVB) SO THESE PATIENTS SHOULD BE EXCLUDED

13) Can you clarify the adverse event reporting requirements (section 15.2 and 15.4)? It is unclear who exactly the local site is suppose to contact, and how, with serious adverse events (should we contact UCSD's IRB directly? Moores Cancer Center DSMB? if so, please provide contact information). Section 15.2 also states that the various IRBs, DSMB, sponsor, etc should be contacted in "a timeframe defined by institutional policy." Our policy states that contacting the sponsor regarding an AE is to be done in the timeframe specified in the sponsor's policy.

SECTION 15.0 WAS MODIFIED TO CLARIFY THE PROCEDURES FOR ADVERSE EVENT REPORTING, INCLUDING WHO TO CONTACT ON THE DATA AND SAFETY MONITORING COMMITTEE. FOR A SERIOUS ADVERSE EVENT, THE LOCAL INVESTIGATOR SHOULD CONTACT BOTH THE STUDY P.I. AND THE CHAIR OF THE DATA AND SAFETY MONITORING COMMITTEE. THIS SECTION IS SUBJECT TO CHANGE OR AMENDMENT BASED ON THE POLICY OF THE SPONSOR.

14) #6.1.3.2 - (Eligibility criteria) - Should we not mandate CT Scan or USG as an essential staging modality for Stage I patients since IA1 and IB2 are distinguishable by a very thin margin that may not be discernable clinically but would have academic implications?

CT OR MRI OR PET/CT IS REQUIRED TO STAGE THE PELVIS (SECTION 6.1.7)

15) Some Typographical errors are mentioned as under as they could pose problems in data entry and retrieval:

1. APPENDIX IV : DHIF (Page 46) - #13 Post-Menopausal - Start (?State) Year of Menopause

BY “START YEAR OF MENOPAUSE” WE MEAN, THE YEAR MENOPAUSE BEGAN
2. APPENDIX V : DEF (Page 48) - #3 finds repetition as both Date of Surgery as well as Estimated Tumor Size

THANK YOU, THIS HAS BEEN CORRECTED

3. APPENDIX VI : TIF (Page 49) - #15 is missing!

THANK YOU, THIS HAS BEEN CORRECTED

16) Could you explain 'Calendar Base Date' (Page 9 : REGISTRATION WORKSHEET under #15)?

CALENDAR BASE DATE IS THE EXPECTED DAY 1 OF TREATMENT (CHEMORADIATION). THIS DATE (DAY 1) THEN CASCADES WHEN EVERYTHING ELSE IS DUE

17) For nodal volume, do you contour the external iliacs and commons from the bifurcation whether that is at L4/5 or L3/4? Also, for presacral nodes, I usually got to the top of S3. Also, you should list CTV1, CTV2 and CTV3 in order, to minimize the chance someone mixes them up.

SECTION 9.2.2 HAS BEEN REWRITTEN TO CLARIFY THE TARGET DELINEATION PROTOCOL IN RESPONSE TO CONFUSION AND INQUIRIES. ALSO, WE ARE POSTING INSTRUCTIONAL VIDEOS FOR HOW TO CONTOUR TARGETS AND NORMAL TISSUES AND GUIDELINES FOR EVALUATING TREATMENT PLANS FOR THIS STUDY ON OUR WEBSITE

18) I would specifically say include or exclude rectum in bowel

SECTION 9.2.3.2 HAS BEEN MODIFIED TO CLARIFY THIS

19) The PTV expansion especially around the vaginal cuff seems too large

SECTION 9.2.2.4 HAS BEEN MODIFIED TO CLARIFY AND SIMPLIFY THE PTV EXPANSIONS

20) In section 9.5 about the QA review, you may want to specify when you’d like the data submitted. A lot of protocols we participate in specify data to be submitted either prior to RT start, within one week of RT start, or within one week of RT Finish

SECTION 9.5.1 WAS MODIFIED TO CLARIFY THIS. CENTRAL PRE-REVIEW OF IMRT IS NOT REQUIRED BUT IS ENCOURAGED FOR THIS STUDY, SO THAT FEEDBACK ON THE PLAN CAN BE GIVEN BEFORE TREATMENT BEGINS. IF THIS IS NOT POSSIBLE, THEN PLANNING DATA SHOULD BE SUBMITTED NO LATER THAN 1 MONTH FOLLOWING COMPLETION OF TREATMENT

21) Who would be responsible for filling out the form Appendix VI (TIF)? Any dosimetry specific forms?
THE DOSIMETRIST, PHYSICIST, PHYSICIAN, CLINICAL TRIAL COORDINATOR, DATA MANAGER, OR P.I. CAN FILL OUT THE FORM. THERE ARE NO FORMS SPECIFICALLY FOR DOSIMETRY, SINCE ALL THIS DATA WILL BE TRANSMITTED ELECTRONICALLY

22) How will you handle output checks at each institution?

INSTITUTIONS MAY BE REQUIRED TO SUBMIT PHANTOM AND OUTPUT MEASUREMENTS FOR CREDENTIALING, DEPENDING ON THE REQUIREMENTS OF THE SPONSOR. THE FIRST KEY STEP IS TO CONDUCT A DRY RUN TO CENTRALLY REVIEW SAMPLE TREATMENT PLANS FROM EACH CENTER

23) Is re-planning allowed?

RE-PLANNING IS ALLOWED AND THIS IS NOW EXPLICITLY STATED IN SECTION 9.2.4.9

24) There is no definition of randomization method or mention of randomization at registration

SECTION 16.1.4 WAS ADDED. PATIENTS ON THE PHASE III TRIAL WILL BE RANDOMIZED AT THE TIME OF REGISTRATION. RANDOMIZATION WILL OCCUR WITHIN STRATA (BLOCK DESIGN).

25) From the statistics the Phase II sounds like a randomized trial; why not just do an interim analysis? There is no mention of an interim analysis or stopping rules. It is stated this is a feasibility study but it is post-hoc feasibility. Shouldn’t that be the role of the Phase II?

THE STUDY IS A PHASE II/III TRIAL, THE PHASE II BEING A SINGLE ARM LEAD-IN STUDY TO ESTIMATE TOXICITY AND FEASIBILITY IN THE INTERNATIONAL MULTI-CENTER SETTING, THE PHASE III BEING A RANDOMIZED TRIAL TO TEST THE EFFECT OF IMRT VERSUS CONVENTIONAL TECHNIQUES. FEASIBILITY IS A SECONDARY ENDPOINT AND IS DEFINED IN SECTIONS 9.5 AND 16.2.2. I DON’T KNOW WHAT POST-HOC FEASIBILITY MEANS VERSUS PRE-HOC

THE PHASE II/III DESIGN IS FAVORED IN THIS SETTING BECAUSE OF THE PROMISING NATURE OF THE EXPERIMENTAL TREATMENT (IMRT) BUT THE NEED TO BUILD IN A CHECK ON THE ASSUMPTION OF LOW TOXICITY WITH IMRT (SEE RUBINSTEIN ET AL. CLIN CANCER RES 2009). PHASE II RANDOMIZED TRIAL DESIGNS ARE PROBABLY MORE SUITABLE FOR DRUG SCREENING TRIALS. A SIZABLE PHASE II COMPONENT IS REQUIRED BECAUSE OF THE NEED FOR PRECISION IN ESTIMATING TOXICITY AND SECONDARY ENDPOINTS IN THE EXPERIMENTAL ARM. ALSO, FEASIBILITY OF THE IMRT TECHNIQUE GIVEN IN THIS TRIAL IS IMPORTANT TO ESTABLISH TO LEAD IN TO A PHASE III TRIAL.

STOPPING RULES WILL BE INCLUDED IN THE AMENDMENT BEFORE PROCEEDING TO THE PHASE III COMPONENT. PHASE II AND III HAVE THE SAME PRIMARY ENDPOINT, BUT PHASE II WILL NOT BE COMBINED WITH PHASE III PATIENTS SINCE THEY ARE NOT RANDOMIZED.
26) Are all the eligibility requirements necessary? The list appears too extensive which may hinder accrual.

WE RE-REVIEWED THE ELIGIBILITY REQUIREMENTS AND ALL ARE DEEMED BOTH NECESSARY AND SUFFICIENT AND ARE STANDARD RELATIVE TO OTHER PROSPECTIVE TRIALS. MANY APPLY TO ELIGIBILITY AND FITNESS FOR CHEMOTHERAPY AND SO THE LIST OF REQUIREMENTS MAY BE LONGER THAN RADIOTHERAPY-ONLY STUDIES

27) This trial is not blinded; there is strong bias possible for IMRT arms

POTENTIAL BIAS DUE TO LACK OF BLINDING IS AN ISSUE. IT WOULD BE EXTREMELY DIFFICULT AND IMPRACTICAL TO BLIND PATIENTS TO THEIR TREATMENT ASSIGNMENT AND IMPOSSIBLE TO BLIND PHYSICIANS TO THE PATIENT’S TREATMENT ASSIGNMENT. IT MIGHT BE POSSIBLE TO BLIND THE EVALUATOR OF TOXICITY/OUTCOMES TO THE TREATMENT ASSIGNMENT, BUT WOULD BE DIFFICULT TO VERIFY THIS IN A MULTI-INSTITUTIONAL TRIAL. ONE SAFEGUARD IS THAT HEMATOLOGIC TOXICITY, WHICH IS A MAJOR COMPONENT OF THE PRIMARY ENDPOINT, IS QUANTITATIVE AND LESS SUBJECT TO BIAS. SMALL BOWEL TOXICITY IS PARTIALLY SUBJECTIVE BUT WE WILL REQUIRE DOCUMENTATION OF TREATMENT PRESCRIBED TO CONFIRM THE SEVERITY.

28) The plans are not reviewed prior to treatment. With so many centers in an international setting this may lead to large problems. All plans need pre-review.

ALL CENTERS WILL COMPLETE BOTH A “DRY RUN” PRIOR TO INITIATING THE TRIAL AND A “WET RUN” (SECTION 8.1) TO ASSURE QUALITY CONTROL OF THE INITIAL FEW PATIENTS. REQUIRING ALL PLANS TO UNDERGO PRE-REVIEW WOULD COMPLICATE THE TRIAL CONSIDERABLY AND MAY BE EXCESSIVE. ALL PLANS ARE ENCOURAGED TO BE SUBMITTED IN ADVANCE FOR PRE-REVIEW AND ARE REQUIRED TO BE SUBMITTED WITHIN 1 MONTH OF CONCLUSION OF TREATMENT

29) In RTOG GI and GU trials the rate of grade 3 toxicity after pelvic RT <5%. CTCAE are not validated and may not be best for the primary endpoint. For example, having 7 bowel movements in one day is equivalent to receiving transfusions for rectal bleeding (both Grade 3). Also this mixes chronic (mostly implant related) and acute toxicity.

THE DEFINITION OF ACUTE TOXICITY WAS CLARIFIED IN SECTION 16.1.1. THE RATES OF GRADE ≥ 3 GI, GU, AND HEMATOLOGIC TOXICITY FOR CONVENTIONAL RT WITH CONCURRENT CISPLATIN-BASED CHEMOTHERAPY FROM 7 LARGE STUDIES ARE 11%, 2%, AND 21%, RESPECTIVELY. IF THESE WERE INDEPENDENT, THE EXPECTED RATE OF ANY TOXICITY WOULD BE 1-0.89*0.98*0.79 = 31%. CTCAE WAS USED IN RTOG 0418 AND SEEMS APPROPRIATE FOR THIS STUDY, WHICH IS DESIGNED TO TEST THE EFFECT OF IMRT. AS TO THE TANGIBLE BENEFIT TO PATIENTS, PATIENT-REPORTED OUTCOMES MIGHT BE DESIRABLE, BUT THERE ARE NO DATA ON THE EFFECT OF IMRT ON PATIENT REPORTED OUTCOMES. A “TANGIBLE BENEFIT” ENDPOINT WOULD BE MORE IMPORTANT FOR A DETERMINANT OR PRACTICE-
CHANGING TRIAL; IN CONTRAST, THIS STUDY SHOULD BE VIEWED AS A KEY COMPONENT OF A SEQUENCE OF TRIALS TO TEST (IN A SUBSEQUENT STUDY) WHETHER IMRT CAN PERMIT MORE EFFECTIVE DELIVERY OF CONCURRENT CHEMOTHERAPY. AS SUCH, IT IS IMPORTANT THAT THERE IS PROMISING PRELIMINARY DATA FROM MODELING STUDIES SUPPORTING AN EFFECT OF IMRT

IT WOULD BE MORE EXACT TO USE GRADE ≥ 3 HEMATOLOGIC TOXICITY AND EITHER GRADE ≥ 2 OR ‘CLINICALLY SIGNIFICANT’ SMALL BOWEL TOXICITY AS PRIMARY ENDPOINTS SINCE THESE ARE ACTUALLY THE ONLY TWO ENDPOINTS FOR WHICH THERE IS VALIDATED EVIDENCE OF AN EFFECT OF DOSE REDUCTION (SPECIFIC TO PELVIC CHEMORT). I RE-ESTIMATED SAMPLE SIZES USING THE COMBINED ENDPOINT OF GRADE ≥ 3 HEMATOLOGIC TOXICITY AND “CLINICALLY SIGNIFICANT” GRADE ≥ 2 GI TOXICITY (DEFINED IN SECTION 16.1.1) AND THE RESULTING ESTIMATES WERE SLIGHTLY SMALLER THAN THOSE OBTAINED USING THE PRIMARY ENDPOINT GRADE 3 HEME / GI / GU TOXICITY. IT SEEMS PRUDENT TO SELECT THE ENDPOINT MOST SPECIFIC TO THE TREATMENT EFFECTS SO THIS WAS CHANGED

30) The statistical section is inadequate. There is no definition of statistical methods used. No stratification

SECTION 16.0 HAD DETAILED DESCRIPTIONS OF STATISTICAL METHODS BUT THIS SECTION WAS FURTHER MODIFIED AS STATED ABOVE TO CLARIFY THE ENDPOINTS, JUSTIFICATION FOR SAMPLE SIZE CALCULATIONS, AND METHODS OF RANDOMIZATION. STRATIFICATION SCHEME WAS STATED IN SECTION 1.0 (SCHEMA) BUT IS NOW INCLUDED IN SECTION 16.1.4 AS WELL

31) Brachytherapy dose and fractionation schemes were unclear. Can you list the acceptable dose and fractionation regimens in the protocol?

SECTIONS 9.4.2.2 AND 9.4.6 WERE MODIFIED TO LIST SPECIFIC ALLOWABLE DOSE/FRACTIONATION SCHEMES. PLEASE REVIEW AND CONFIRM THESE AGREE WITH YOUR INSTITUTIONAL STANDARD(S).

32) For radical treatment you recommend 45Gy of EBRT and 5x6 Gy of brachytherapy, BUT you need maximum 61 Gy of final bioequivalent dose to the rectum, and 70 Gy for the bladder ICRU point? Even if I have maximum 70% of dose prescribed to the point A at the rectal reference point (it means 5x 4,2Gy) - the equivalent final dose to the rectum will be more than 73 Gy. The same is for the bladder.

SECTION 9.4 WAS MODIFIED TO CLARIFY BRACHYTHERAPY AND CUMULATIVE NORMAL TISSUE DOSES; PLEASE REVIEW AND DETERMINE IF THESE CONFORM WITHIN YOUR INSTITUTIONAL PROTOCOLS OR GUIDELINES

33) Do you insist on a parametrial boost?

SECTION 9.2.4.8 WAS MODIFIED TO CLARIFY – THIS IS LEFT TO THE DISCRETION OF THE TREATING PHYSICIAN AND IS NOT MANDATORY

34) Is the application of fiducial markers to vaginal fornix before planning CT required?
SECTION 9.2.1.2 WAS MODIFIED TO CLARIFY – THIS IS OPTIONAL

35) Would you accept if we use HDR brachytherapy prescribed to the point A, with CT planning and volumic optimisation to the 2cc of OAR (we can report the dose to ICRU referent points as well)?

THIS IS ACCEPTABLE PROVIDED THE REQUIREMENTS IN SECTION 9.4.2.2 AND 9.4.2.4 ARE MET

36) Who will pay all the MRI or PET/CTs on follow-up visits? These are usually paid by the sponsor of the clinical study.

FOLLOW-UP MRI AND PET/CT ARE NOT REQUIRED; CHEST X-RAYS AND PELVIC CTS ARE ACCEPTABLE. ROUTINE FOLLOW-UP IMAGING SHOULD BE PAID BY THE SUBJECT’S INSURER. IF YOU FORESEE THIS AS A PROBLEM, PLEASE SUBMIT A SUPPLEMENTAL BUDGET REQUEST

37) Is there any salary for researchers?

NO SALARY SUPPORT FOR RESEARCHERS IS REQUESTED. COMPENSATION OF $1500 PER SUBJECT WILL BE REQUESTED FROM THE SPONSOR TO BE PAID TO THE SUBJECT’S INSTITUTION TO OFFSET COSTS. IF ADDITIONAL FUNDS ARE NEEDED TO OFFSET OTHER COSTS, PLEASE SUBMIT A SUPPLEMENTAL BUDGET REQUEST.

38) Can you clarify guidelines for the upper border of the CTV?

GUIDELINES WERE CLARIFIED; SEE SECTION 9.2.2.3

39) Please specify that fusion of the MRI or PET should be in the treatment position

SECTION 9.2.2.1 WAS SO AMENDED

40) In section 9.2.3.6 – can you clarify technique for femoral head delineation

SECTION 9.2.3.6 WAS CLARIFIED

41) Should heterogeneity corrections be applied? Should you specify that the max dose should occur within the PTV

SECTIONS 9.2.4.4 AND 9.2.4.10 WERE AMENDED / ADDED

42) Is radical IMRT allowed in place of a brachytherapy boost?

IMRT IN PLACE OF BRACHYTHERAPY IS DISALLOWED (SEE SECTION 9.2.7)

SUBSEQUENT TO PROTOCOL FINALIZATION (4/30/11)

AMENDMENT #1 – ITV (5/2/11)
43) The margin around the vaginal cuff for postoperative patients seems too small. Will you require the use of an ITV?

THE INITIAL MARGIN SELECTED WAS CONSISTENT WITH PRIOR PROTOCOLS (E.G. GOG258). HOWEVER, WE AGREE THE MARGIN AROUND THE CUFF SHOULD BE EXPANDED. THEREFORE SECTION 9.2.2.3 WAS CLARIFIED THAT FOR POSTOPERATIVE PATIENTS THE VAGINAL CUFF SHOULD BE CONTOURED AS CTV1 AND THEREFORE A 1.5 CM MARGIN SHOULD BE APPLIED. PREVIOUS STUDIES SUGGEST THIS MARGIN SHOULD BE ADEQUATE PARTICULARLY IF DAILY VOLUMETRIC IGRT IS BEING IMPLEMENTED, ALTHOUGH ADMITTEDLY DATA IN THIS AREA IS STILL LIMITED. FOR PATIENTS THAT WILL NOT RECEIVE DAILY VOLUMETRIC IGRT THE USE OF AN ITV IS ENCOURAGED. THIS TECHNIQUE IS DESCRIBED IN THE NEW SECTION 9.2.2.5 AND AN INSTRUCTIONAL VIDEO WILL BE AVAILABLE FOR DOWNLOAD. AS THE MAJORITY OF PARTICIPATING CENTERS HAVE NOT PREVIOUSLY BEEN IMPLEMENTING AN ITV THIS PRACTICE IS NOT MANDATORY, ALTHOUGH STRONGLY ENCOURAGED.

AMENDMENT #2 – QOL (5/10/11)

44) I don’t see a 6Gy x 5 fx for HDR brachytherapy which is most common regimen we use

THIS WAS AN OVERSIGHT; 6 GY X 5 IS ALLOWED; SECTION 9.4.2.2 WAS MODIFIED

45) There is no background section for QOL, or sample size estimates and analysis plan for QOL. Is QOL being completed for both phase II and III portions? Is accrual to QOL expected to vary by country? When do you expect peak toxicity to occur post treatment? If you expect it at 1 week post-tx and want to correlate peak toxicity with QOL you might want to add an assessment of QOL at 1 week post treatment. You could drop the 8, 18, and 30 month assessments to reduce cost. The selected assessment schedule is not well justified.

SECTION 4.4 WAS ADDED TO PROVIDE BACKGROUND FOR QOL ANALYSIS. SECTIONS 16.2.6 AND 16.3.7 WERE ADDED TO DESCRIBE EXPECTED COMPLIANCE AND SAMPLE SIZES AND PLAN FOR QOL ANALYSIS, INCLUDING CONSIDERATION OF REGIONAL VARIATIONS. 1 MONTH POST-TREATMENT ASSESSMENT WAS ADDED AND 8, 18, AND 30 MONTH ASSESSMENTS WERE DROPPED. JUSTIFICATION FOR THE CHOSEN SCHEDULE WAS ADDED TO SECTION 14.8.

AMENDMENT #3 – SUBSTUDY BACKGROUND (5/28/11)

46) Cisplatin will be given for 5 cycles, not 6 cycles as in GOG trials. The NCIC trial, which treated patients with 5 cycles of weekly cisplatin showed no benefit of concurrent chemo/rt vs rt alone. No background on substudies is given.

THE GOG TRIALS ALLOWED “UP TO 6 CYCLES”. IN THE STUDY BY ROSE ET AL. ABOUT HALF OF THE PATIENTS RECEIVED < 6 CYCLES; IN THE STUDY BY KEYS ET AL., IT DOES NOT SAY HOW MANY GOT 6, ONLY THAT 90% RECEIVED
For a toxicity study, it is imperative to hold the number of cycles of chemotherapy constant, so I would favor keeping to 5 cycles, which is fairly standard in practice. There is one study (Nugent et al.) that found better outcomes in patients receiving 6 cycles vs. < 6 cycles, but this could be due to selection bias.

Sections 4.5 and 4.6 were added to provide background for the image-guided bone marrow sparing and KV CBCT substudies. Section 16.2.5 was expanded to describe expected power in the substudies. References were re-numbered and new references added and updated in Section 17.0.

Amendment #4 – 16.2.2 Update (5/28/11)

Sections 16.2.2 was changed to clarify expected duration of accrual.

Amendment #5 - Update to Consent Form and Data Forms (6/10/11)

Sample Consent Form Changed

Demographic and Health Information Form

Question 4
- Update marital status options to include "single" and remove "divorced/separated":
  - Marital Status: Single, Married, Living as married, Divorced, Separated, Unknown / Declined to State

Question 8
- Change question to ask the patient to specify currency for Yearly Household Income
  - Questions 9 and 10
  - Change the "(skip to question #11)" and "(skip to question #12)" to "(skip to question #10)" and "(skip to question #11)" respectively.
  - Change 9a "Yes, currently drinking (Answer B, C, D, E)" to "Yes, currently drinking (Answer B, C, D, E)"
  - Change 10a "Yes, currently smoking (Answer B, C, D, E)" to "Yes, currently smoking (Answer B, C, D, E)"

Symptoms and Toxicity Form

Question 1
- typo: "1. Instructions: Grades symptoms in all categories" should be "Grade symptoms in all categories"
- grade "8" (not-evaluable) is missing under the column GRADES for all toxicities
- For toxicity "Gastrointestinal Other" and "Genitourinary Other":
  - "i.e." should be "e.g."
  - 'obstruction' should be 'obstruction'

Outcomes Evaluation Form

Question 6
- There are two questions numbered "6". The form should be renumbered to go to "9".
Quality of Life Assessment Form
- Forms in all languages are out of order. This error is only on the website so nothing in the protocol needs to be updated. I attached the updated QOLA forms for Rich to upload.
- There are no QLQ-CX24 form translations in Czech, Mandarin, Thai, or Vietnamese. The EORTC website (http://groups.eortc.be/qol/translations.htm) lists them as unavailable.

AMENDMENT #6 - UPDATE TO CONSENT FORM AND DATA FORMS (6/24/11)

HARD CONSTRAINTS FOR BOWEL, RECTUM, BLADDER, FEMORAL HEADS CHANGED TO 110% (SECTION 9.2.4.6)

AMENDMENT #7 – RESPONSES TO UCSD IRB (7/15/11)

1. This protocol is described as a phase II/III protocol, but the two phases are not well and clearly separated. The primary endpoint is to compare rates of toxicity (bone marrow and GI) between IMRT and standard XRT, which easily applies to the randomized phase III portion, though section 16.2.1 implies that the phase II portion will also test toxicity against published rates. Section 16.3.2 alludes to feasibility at the various sites. Is this the real endpoint of the phase II study? To put it simply, what is the real purpose of the phase II study and how will the decision to move on to the phase III study be made? Please revise the Research Plan to clarify.


2. For the phase II portion, please revise the Research Plan to include clearly defined stopping rules (based on toxicity or feasibility, etc.). For example, if there are site(s) performing poorly with respect to adherence to protocol specifications (as defined in 16.3.2), will they be prevented from further enrollment? If the majority of sites perform poorly, will the whole study be halted because it will be deemed not "feasible" as defined in section 16.3.2? If there is higher than expected toxicity, will the protocol be stopped? Answers to these questions need to be pre-specified in the Research Plan and Master Protocol.

AT THE COMPLETION OF PHASE II, A PROTOCOL AMENDMENT WILL BE ISSUED DEFINING THE STOPPING RULES, AS STATED IN SECTION 16.2.1. SECTION 16.3.2 WAS AMENDED TO CLARIFY THAT FEASIBILITY WILL BE
ASSESSED AT THE END OF PHASE II AND THAT IF FEASIBILITY AT AN INSTITUTION IS NOT DEMONSTRATED, THEN ENROLLMENT ON PHASE III WILL BE SUSPENDED FOR THAT INSTITUTION. NOTE THAT FEASIBILITY OF IMRT IS HIGHLY LIKELY TO BE DEMONSTRATED, GIVEN THAT PARTICIPATING CENTERS ALREADY ARE USING IMRT. TOXICITY IS EXPECTED TO BE SIGNIFICANTLY LOWER WITH IMRT THAN CONVENTIONAL RT. IF TOXICITY IS SIGNIFICANTLY HIGHER THAN PUBLISHED RATES IN THE LITERATURE THEN THE FEASIBILITY OF PHASE III WILL BE REFLECTED IN THE REVISED SAMPLE SIZE. SECTION 16.2.1 WAS AMENDED TO STATE THAT FEASIBILITY OF PHASE III WILL BE ASSESSED BASED ON THE REVISED SAMPLE SIZE AND AVAILABLE FUNDING.

3. Research Plan item 13. Alternatives to Study Participation should list participation in other clinical trials or receiving other chemotherapy/radiation options per the treating physician.

RESEARCH PLAN WAS MODIFIED

4. Facepages: please correct number of expected accruals (says 0).

FACEPAGE WAS MODIFIED; EXPECTED ACCRUAL AT UCSD IS 20

5. Please revise to fill out all sections of Research Plan rather than simply referring to Master.

RESEARCH PLAN WAS MODIFIED

6. In the Master section 10.2.2 under cisplatin dose reduction guidelines, it says that cisplatin will be resumed at a reduced dose after being held for nausea or renal failure. Please revise to define resolution of these symptoms (grade 1? grade 2?).

SECTION 10.2.2 WAS AMENDED

7. In the Master under criteria for removal from protocol therapy, it says, "Adverse event requiring removal from study." Please revise Master to specify how adverse events will be evaluated for this criteria (CTCAE grade, or prespecified toxicities, etc.).

SECTION 15.5 WAS AMENDED. NOTE, THIS IS SPECIFIED IN SECTION 15.5

8. Note to PI: the inclusion protocol refers to Zubrod performance status, but the appendix has the Karnofsky scale.

SECTION 6.1.8 WAS AMENDED.
9. Please revise the Research Plan to clarify how it will be determined which subjects participate in which substudy(s). How many will be in each substudy? How do you arrive at these numbers?

All subjects’ data will be used in substudy 1. Substudy 2 will be limited to data collected from sites submitting daily CBCT data. Substudy 3 will be limited to data collected from centers able to administer functional BM-sparing IMRT. Centers will declare in advance whether they intend to enroll patients on the daily CBCT substudy and/or the functional BM-sparing IMRT substudy.

RESEARCH PLAN SECTION 9 WAS MODIFIED TO REFLECT THIS AND MASTER PROTOCOL SECTION 16.7 WAS AMENDED

10. Please revise the Master and Research Plan to provide more detail on how oversight of other centers will be performed. For example, please provide information on how reports of AEs will be disseminated to the various sites for submission to their own IRBs. Here is guidance from the IRB instructions: "be shared among all sites and appropriate agencies including safety updates, interim results, or other information that may impact risks to subjects or others; modifications to the protocol and/or consent; etc." Click on or paste the following address to your browser for a copy of the application instructions:

Whenever there is an adverse event reported or a protocol amendment or change in the consent form or interim results or other information that may impact the risks to subjects or others, the study PI and/or coordinator at UCSD will notify all the institution’s PI’s and study coordinators via email.

RESEARCH PLAN SECTION 9 WAS MODIFIED TO REFLECT THIS AND IN THE MASTER PROTOCOL SECTION 15.9 WAS ADDED
11. Revise/clarify the Consent as follows:
   a. This study is for women with cervical cancer, but the Consent lists sterility for men and impotence as potential risks. Please remove all references to male subjects.
   b. Please revise risks of chemotherapy to use lay language for: bone marrow suppression, malaise, skin toxicity, muscle toxicity, etc.
   c. Please revise the Consent to specify throughout the document that the chemotherapy is cisplatin.
   d. The consent says that subjects may choose not to be informed of HIV testing results. If HIV positive, it must be reported to the board of health and can be put in the patient's medical record without patient consent. California law allows patients to refuse HIV testing. Please clarify: will subjects be allowed to refuse testing (if so, include this in the consent); if a subject chooses not to be informed of her results, how will this logistically be accomplished if it goes in the chart? Is it ethical to allow an HIV positive subject to refuse the results if it means that she can then carry out behavior that puts others at risk?
   e. The consent includes risks of tumor biopsy, but presumably this will have been performed prior to consideration of study enrollment as part of standard of care. Please remove from consent.
   f. There is a large paragraph about risks if subjects become pregnant while on study. Since the majority of subjects will have had hysterectomy, please clarify that this only applies to those with unresectable disease who have not had hysterectomy so subjects can better understand.
   g. Under alternatives to participation, please include radiation as standard of care and off study, including IMRT if, as stated in the consent, IMRT is already in use for the care of cervical cancer patients.
   h. Subjects are also asked to give optional consent for a "daily imaging procedure," but this is never explained or described. Please do so.
   i. Revise the Consent to include procedures for orderly termination of subject's involvement in study.

THE CONSENT FORM WAS AMENDED IN RESPONSE TO THESE REQUESTS

1. Which statistical test is used to determine the statistical power of this study? This was not indicated in the sample size section of the protocol.
2. DSMB composition typically includes a biostatistician to assist in the analysis of safety and efficacy data during clinical trial monitoring. Consideration should be given to adding a biostatistician to the DSMB empanelled at UCSD to oversee this multi-site trial.

THE STATISTICAL TESTS ARE ONE- AND TWO-SAMPLE BINOMIAL TESTS FOR PROPORTIONS. SECTION 16.2 WAS AMENDED.

DR. JEONG WAS ADDED TO THE DSMB AND THE PROTOCOL FACESHEET WAS MODIFIED
Please clarify the following items regarding the radiological procedures involved in this study protocol and make revisions to the Research Plan and Consent where applicable. SEND YOUR RESPONSE AND THE REVISED DOCUMENTS TO herc@ucsd.edu FOR RADIATION SAFETY REVIEW.

1) In the Research Plan, Item 14 Potential Risks, please include a Radiation Exposure paragraph. This is used to summarize the radiation use and justify the cumulative exposure quoted in the Consent. In this study, participants are likely to receive CT, PET/CT or MRI of the chest/abdomen/pelvis at screening and months 4, 8, 12, 18, 24, 30 & 36. The cumulative exposure may be up to 8 CT (104 mSv) and 8 FDG-PET (176 mSv), for a total of 280 mSv. This supports the 280 mSv quoted in the Consent. Also note that IMRT exposure may be 45-50 Gy.

2) Also, in the Research Plan, please clarify whether study participants may be enrolled in the Functional Bone Marrow Sparing Substudy (substudy 3, Master Protocol section 9.2.3.7 & 9.7). If so, please clarify the PET technique to be used, the frequency, and include in the cumulative radiation exposure.

3) In the Informed Consent, Risks from X-rays and/or Scans section, please replace the older wording with the current template. Note the therapy dose reference is included, but the appropriate units (for therapy only) are Gy. In the second paragraph, please indicate whether all/most/some none of the imaging is standard care (assumption below is ‘all’). The radiation risk statement for this study could read as follows.

“During your participation in this research study, you may be exposed to radiation from CT and PET scans. The total exposure from these imaging studies is calculated to be approximately 280 mSv. This amount is more than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future.”

“The principal investigator for this research study has determined that all of the imaging prescribed for this study would typically be performed as part of the standard medical care. Radiation exposure may be decreased if non-radiation alternatives are used, such as MRI. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, Dr. Loren Mell, or your regular doctor.”

“Note that exposure you will receive from diagnostic procedures, however, is much less than the exposure you will receive from treatment, which is 45-50 Gy.”

THESE CHANGES WERE MADE TO THE RESEARCH PLAN AND CONSENT FORM

AMENDMENT #8 – CHANGES TO CONSENT FORM IN RESPONSE TO UCSD IRB (8/12/11)

CHANGES WERE MADE TO CONSENT FORM
AMENDMENT #9 (2/23/12)

SECTION 9.2.4.6: HARD CONSTRAINTS ON BOWEL, BLADDER, RECTUM, FEMORAL HEADS CHANGED TO MAXIMUM < 115%

AMENDMENT #10 (3/8/12)

CONTACT INFORMATION WAS UPDATED

MINOR CHANGES TO WORDING / CLARIFICATION OF ELIGIBILITY CRITERIA AND SCHEDULE OF EVENTS

REMOVED/UPDATED CRF APPENDICES