RTOG 1203: A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

Fast Facts

PATIENT SELECTION

Conditions for Patient Eligibility

3.1.1 Pathologically proven diagnosis of endometrial or cervical cancer

3.1.2 Patients must have undergone a hysterectomy (total abdominal hysterectomy, vaginal hysterectomy or radical hysterectomy or total laparoscopic hysterectomy) for carcinoma of the cervix or endometrium within 49 days prior to registration. Performance of a bilateral salpingo-oophorectomy will be at the treating surgeon’s discretion.

3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following diagnostic workup:
   - History/physical examination within 45 days prior to registration;
   - CT, MRI or PET-CT including the abdomen and pelvis should be performed for initial radiological staging. This may be performed pre- or post-surgery within 90 days prior to registration. Imaging performed post-operatively should show no evidence of residual disease. Any evidence of malignancy identified on pre-operative imaging should have been completely resected surgically prior to protocol treatment.
   - Chest CT or chest x-ray must be performed within 90 days prior to registration (unless a PET-CT has been performed)

3.1.4 Zubrod Performance Status 0-2

3.1.5 Age ≥ 18

3.1.6 CBC obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3;
   - Platelets ≥ 100,000 cells/mm3;
   - Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.7 For patients receiving chemotherapy:
   - Serum creatinine ≤ 1.5 mg/dL and calculated creatinine clearance ≥ 50 cc/min. Both tests must be within these limits. The creatinine clearance should be calculated using the Cockcroft-Gault formula: (See Section 7.3.1)
   - AST ≤ 2 x ULN
   - Bilirubin ≤ 2 x ULN
   - Alkaline phosphatase, Mg, BUN and electrolytes must be obtained and recorded

3.1.8 Endometrial Cancer:
   - Patients with the following histologic features are eligible for pelvic radiation therapy without weekly cisplatin:
     - <50% myometrial invasion, grade 3 adenocarcinoma without uterine serous carcinoma (USC) or clear cell histology
     - ≥50% myometrial invasion grade 1-2 adenocarcinoma without USC or clear cell histology
   - Patients with the following histologic features may be treated with pelvic radiation with or without weekly cisplatin. The decision to add weekly cisplatin for these patients is at the treating physician’s discretion:
     - FIGO 2009 stage II endometrial cancer of any grade including USC and clear cell carcinoma.
     - FIGO 2009 IIIC1 (pelvic lymph node positive only, para-aortic nodes sampled and negative if removed) including USC and clear cell carcinoma. NOTE: if para-aortic nodes are not removed, CT abdomen or PET-CT must demonstrate no evidence of lymphadenopathy
3.1.9 Cervical Cancer:

- Patients with the following pathology findings may be treated with pelvic radiation with or without weekly cisplatin at the treating physician’s discretion. The decision to add weekly cisplatin for these patients is at the treating physician’s discretion.
  
  o Patients with intermediate risk features including two of the following histologic findings after radical hysterectomy:
    - 1/3 or more stromal invasion
    - Lymph-vascular space invasion
    - Large clinical tumor diameter (> 4 cm)
  o Patients with cervical cancer treated with a simple hysterectomy with negative margins

- Patients with any of the following criteria following radical hysterectomy are eligible for this study and must receive weekly cisplatin:
  
  o Positive resected pelvic nodes and para-aortic nodes negative if removed Note: if para-aortic nodes are not removed, CT abdomen or PET-CT must demonstrate no evidence of lymphadenopathy
  o Microscopic parametrial invasion with negative margins

3.1.10 Patient must provide study specific informed consent prior to study entry.

3.1.11 Willingness and ability to complete the bowel and urinary domains of the EPIC prior to registration

**Conditions for Patient Ineligibility**

3.2.1 Patients with para-aortic nodal disease or who require extended field radiotherapy beyond the pelvis.

3.2.2 Patients with histology consisting of endometrial stromal sarcoma, leiomyosarcoma or malignant mixed mullerian mixed tumor (MMMT or carcinosarcoma)

3.2.3 Patients who exceed the weight/size limits of the treatment table or CT scanner.

3.2.4 Mental status changes or bladder control problems that make the patient unable to comply with bladder-filling instructions.

3.2.5 Patients with evidence of metastatic disease outside of the pelvis.

3.2.6 Patients with positive or close (< 3 mm) resection margins

3.2.7 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.

3.2.8 Prior radiation therapy to the pelvis

3.2.9 Patients with active inflammatory bowel disease.

3.2.10 Severe, active co-morbidity, defined as follows:
  
  - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
  - Transmural myocardial infarction within the last 6 months
  - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
  - Other major medical illness which requires hospitalization or precludes study therapy at the time of registration
  - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory test coagulation parameters are not required for entry into this protocol
• Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

3.2.11 Patients with prior treatment with platinum-based chemotherapy

3.2.12 Women who are breastfeeding

PRETREATMENT EVALUATIONS/MANAGEMENT
NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. See Appendix II for a summary of study assessments and time frames.

• Physical exam, performance status/weight
• Hysterectomy ≤ 49 days
• Chest CT or chest x-ray
• Abd/Pelvic CT, MRI or PET/CT
• CBC w/ differential
• CMP and magnesium for patients receiving chemotherapy per Section 3.1.7
• Blood for Translational Research (if patient consents)
• Tissue for Translational Research (if patient consents)

4.1 Required Evaluations/Management
• Completion of the bowel and urinary domains of EPIC is mandatory for all patients (see Section 3.1.11)
• Assessment of weight

4.2 Highly Recommended Evaluations/Management
• Formal consultation by nutritionist
• Audiogram at baseline and following treatment at the discretion of the treating physician for patients who are planned to receive concurrent chemotherapy
• Completion of the FACT-Cx, PRO-CTCAE item for GI toxicity and EQ-5D (for patients who consent to the optional quality of life (QOL) component of the study). Note: If the patient consents to participate in the optional QOL component of the study, sites are required to administer the baseline FACT Cx, PRO-CTCAE item for GI toxicity, and EQ-5D prior to the start of protocol treatment.

TREATMENT
Active Comparator: Arm I
• Patients undergo standard (3-dimensional) radiation therapy 5 days a week for up to 5.5 weeks.

Experimental: Arm II
• Patients undergo intensity-modulated radiation therapy (IMRT) 5 days a week for up to 5.5 weeks