Enrolling Clinical Trials: Dose Escalation of Neoadjuvant Proton Radiotherapy in Esophageal Cancer

Radiation oncologists at the Roberts Proton Therapy Center and the Abramson Cancer Center are conducting a clinical trial [1] to investigate the use of preoperative carboplatin/paclitaxel in combination with proton therapy followed by surgery for the treatment of locally advanced esophageal cancer.

Esophageal cancer is the third most common gastrointestinal malignancy. There are two histologies—adenocarcinoma and squamous cell carcinoma—both prevalent in North America. The primary treatment at every stage is surgery (transhiatal or transthoracic esophagectomy), often in combination with chemotherapy and radiotherapy. With the publication of the CROSS trial, trimodality therapy comprising preoperative chemoradiotherapy (CRT) followed by surgery became the treatment of choice for locally advanced esophageal cancer.

The CROSS trial found a significant benefit for CRT followed by surgery versus surgery alone, with a median overall survival of 49.4 months in the CRT-surgery group versus 24.0 months in the surgery group. Rates of recurrence were also substantially lower in the CRT-surgery group.

Surgery is a mainstay of curative therapy in esophageal cancer, but is associated with post-operative morbidity and occasional mortality, even in experienced hands. In order to develop a strategy to avoid surgery, improvements in CRT complete response rates (currently 25%-40% at the time of surgery) will need to be substantially improved. Additionally, criteria will need to be developed to determine which patients may benefit from the preclusion of resective therapy.

The Role of Imaging
Bio-imaging molecular markers, such as 18F-FDG (fluorodeoxyglucose) PET, and biomarkers (e.g., circulating tumor cells) may be able to identify patients who respond favorably to treatment. For patients with esophageal cancer, the use of 18F-FDG PET as part of the initial work-up is considered standard for identifying metastatic disease. 18F-FDG PET is also commonly used after chemoradiation to see if metastatic disease has developed prior to surgery. It is possible that interim 18F-FDG PET/CT scans during CRT may help predict responders.

Proton Therapy in Esophageal Cancer
The treatment of esophageal cancer with standard radiation is complicated by the organ’s proximity to a number of critical radiosensitive organs, including the heart and lungs. Proton therapy provides an improvement over standard radiotherapy in its ability to deliver a high dose to tumor targets while maintaining lower doses to surrounding normal tissues. This is possible because proton radiation has a rapid dose fall-off at the distal edge of the target (Bragg-Peak effect), a characteristic that allows for significant reductions in radiation dose to normal organs and the potential for dose escalation.

Methods: Patients will be treated with preoperative chemoradiation followed by surgical resection. Concurrent chemoradiation will consist of weekly carboplatin/paclitaxel for 5 weeks, from start until completion of proton therapy. Radiation therapy dose will be escalated to determine the MTD using a 3+3 phase I study design. Patients will receive once daily proton radiotherapy; There will be two target volumes: a larger elective volume and a boost volume to cover the gross tumor plus additional margin. This boost volume will be treated with the dose escalation schema. Patients will have surgery 4 - 8 weeks after completion of chemoradiotherapy. Ancillary studies include collection of patient serum for analysis of CTCs, as well as 18F-FDG PET imaging at week 4. However, 18F-FDG PET imaging pre-treatment and ~4 weeks after chemoradiotherapy; to evaluate the utility of mid-treatment 18F-FDG PET imaging at week 4 as a molecular imaging marker to predict treatment response to chemoradiotherapy; and to assess the utility of circulating tumor cells as biomarkers to predict treatment response to chemoradiotherapy.

Investigating Preoperative Proton Radiotherapy in Esophageal Cancer at Penn

Background: A clinical trial of proton therapy in the setting of preoperative radiotherapy for esophageal cancer. This trial seeks to determine the maximally tolerated radiation dose of dose-escalated proton radiotherapy and to assess the utility of bio-imaging molecular markers to identify patients who will respond favorably to treatment.

Objectives: To identify the maximally tolerated radiation dose (MTD) of dose-escalated proton radiotherapy in combination with carboplatin/paclitaxel in the preoperative setting for esophageal cancer; to estimate pathologic response rates by esophagectomy surgical specimens after escalated doses of chemoradiotherapy; to evaluate the utility of mid-treatment 18F-FDG PET imaging at week 4 as a molecular imaging marker to predict treatment response to chemoradiotherapy; and to assess the utility of circulating tumor cells as biomarkers to predict treatment response to chemoradiotherapy.

Inclusion Criteria:
- Patients with esophageal cancer to be treated with concurrent preoperative chemoradiation with carboplatin and paclitaxel.
- Patients will be treated with preoperative chemoradiation followed by surgical resection. Concurrent chemoradiation will consist of weekly carboplatin/paclitaxel for 5 weeks, from start until completion of proton therapy. Radiation therapy dose will be escalated to determine the MTD using a 3+3 phase I study design.
- Patients will receive once daily proton radiotherapy; There will be two target volumes: a larger elective volume and a boost volume to include the gross tumor plus additional margin. This boost volume will be treated with the dose escalation schema. Patients will have surgery 4 - 8 weeks after completion of chemoradiotherapy.
- Ancillary studies include collection of patient serum for analysis of CTCs, as well as 18F-FDG PET imaging at week 4. However, 18F-FDG PET imaging pre-treatment and ~4 weeks after chemoradiotherapy are standard of care and are not research procedures.

Contact: The principal investigator for this trial is John Plastaras, MD, PhD. For information, prospective patients and/or their clinicians may call 215-615-8078, or email PennCancerTrials@emergingmed.com

1. ClinicalTrials.gov Identifier: NCT02213497. Available at: http://1.usa.gov/1H8emls
Faculty Team

Among the largest and most respected programs in the world, Penn Radiation Oncology offers a variety of innovative treatment options to patients with cancer. In addition, as a national leader in basic science, translational research and clinical trials, Penn Radiation Oncology offers patients access to the latest treatment options—including proton therapy—before they are widely available elsewhere.

Performing Clinical Research in Proton Therapy for Esophageal Cancer at Penn Medicine

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