Radiation Oncology Consultants

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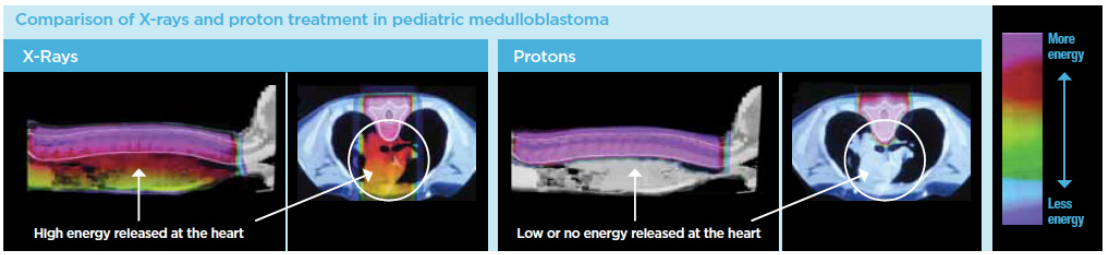
ROC January 2014 Newsletter – Proton Therapy Site Updates

The CDH Proton Center has been treating patients since late 2010. In three years, the center has treated over 1,300 patients. The CDH Proton Center has one of the most complex case mixes of any proton center in the country and has built a strong foundation for future growth and exceptional patient care. The focus of this month's ROC Newsletter is an annual tumor site specific update of diseases treated at the CDH Proton Center with discussions involving pediatric, CNS, thoracic, gastrointestinal, prostate, and breast malignancies.

Pediatric Malignancies

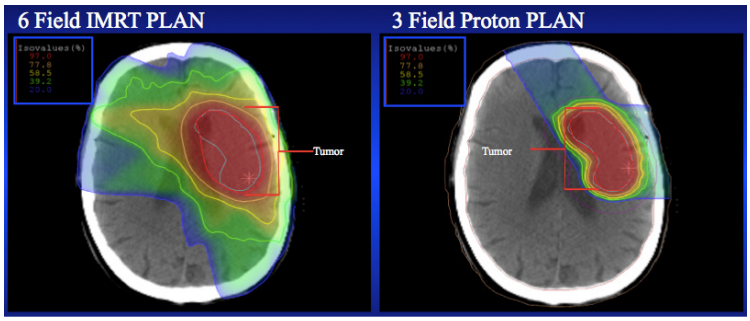
Pediatric cancer treatments are advancing along with the resultant cure rates. At times, however, the more aggressive treatments are leading to more side effects both short term and long term. Proton therapy has been the recent beacon in the darkness of increased toxicity. While providing equivalent efficacy to that of conventional radiation therapy, proton therapy delivers lower doses to surrounding structures, thereby lowering the risk of these toxicities (1).



Source: Jay Loeffler, MD MGH/NPTC

For our pediatric patients, we offer the full spectrum of clinical and supportive oncologic care. Consultations are approached in the multidisciplinary fashion with a team approach in partnership with Lurie Children's Hospital of Chicago (LCHC). Clinical specialties involved include, but are not limited to: hematology oncology, radiation oncology and surgical oncology along with pediatric anesthesia/critical care if necessary. Supportive services in social work, nutrition, along with physical, occupational and speech therapy are also available. In 2013, we treated 63 pediatric patients with proton beam therapy. Twenty-seven of those patients required anesthesia to complete their therapy. We have treated the full spectrum of pediatric neoplasms in the brain, skull base, meninges, soft tissues and lymph nodes.

We participate in numerous phase I-III trials for childhood cancers through the multi-institutional national cooperative groups: Children's Oncology Group and the Pediatric Brain Tumor Consortium. We are also deeply involved in evaluating and improving patient's long term quality of life (QOL) by enrolling them into 2 large studies: LCHC's NCI sponsored patient/parent-reported QOL survey and the NIH sponsored multi-institutional physician reported QOL study.



We strive in every way possible to provide most advanced cancer care to children for cure of their malignancies and to maintain long term QOL. A number of studies have demonstrated the effectiveness of proton therapy and its cost effectiveness vs. standard radiation especially in pediatric brain tumors (2,3). Maximizing treatment dosage and efficacy, while also minimizing normal tissue damage are the ultimate goals of this advanced radiation modality, which we intend to further with research.

Adult Central Nervous System Malignancies

Proton therapy for adult primary central nervous system (CNS) malignancies is an integrated part of the Cadence Brain Tumor Center, a multi-disciplinary neuro-oncology program that features world-class neuro-oncologic, radiotherapeutic and neurosurgical expertise, advanced technology and cutting-edge clinical trials.

Comprising approximately 15% of all patients treated at the CDH Proton Center, the majority of adult patients with primary CNS malignancies are referred from Radiation Oncologists, Neuro-Oncologists and Neurosurgeons throughout the Midwest. Less than 20% of patients who call the center to inquire about the role of proton therapy for their CNS malignancies are deemed clinically appropriate.

The most common CNS indications for the use of proton therapy in adults include:

1) Dose-escalation close to critical structures (i.e., chordomas or chondrosarcomas)
2) Craniospinal irradiation for medulloblastomas, pineoblastomas, etc.
3) Spinal irradiation for myxopapillary ependymomas, sacral schwannomas, etc.
4) Partial brain irradiation for tumors with favorable prognosis (i.e., meningiomas, ependymomas, low-grade gliomas, pituitary adenomas, etc.) in younger patients.

The CDH Proton Center seeks to address important scientific questions exploring the potential benefit of proton therapy in emerging indications through the following multi-institutional clinical trials:

RTOG 1205: Randomized phase II trial of concurrent bevacizumab and re-irradiation versus bevacizumab alone as treatment for recurrent glioblastoma.
ClinicalTrials.gov Identifier: NCT01730950
Currently recruiting participants

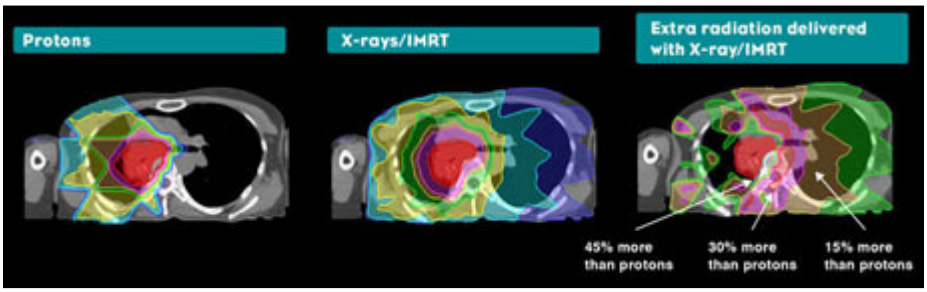
NU_11CO1: Phase II study of the efficacy of hypofractionated radiation therapy with bevacizumab and temozolomide followed by maintenance temozolomide and bevacizumab for recurrent high-grade gliomas.
ClinicalTrials.gov Identifier: NCT01478321
Currently recruiting participants

NRG BN001: Randomized phase II trial of hypofractionated dose-escalated photon IMRT or proton beam therapy versus conventional photon irradiation with concomitant and adjuvant temozolomide in patients with newly diagnosed glioblastoma
Expected to be activated in 2014

In addition, all patients with CNS malignancies are enrolled on the Proton Collaborative Group (PCG) prospective registry to facilitate the reporting of short- and long-term outcomes of proton therapy.

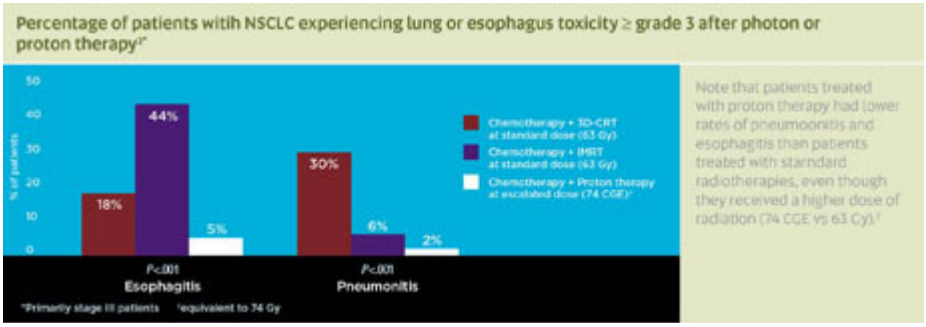
Thoracic Malignancies

Combined chemotherapy and radiation is the standard of care for stage III lung cancer. Proton therapy in this setting offers unique advantages over standard radiation. Studies have shown that despite the use of higher doses of radiation with proton therapy, there is a lower risk of radiation related side effect with a potential improvement in overall survival. The lower incidence and severity of lung and esophagus toxicity afforded by protons translates into therapy that is better tolerated by patients in both the acute and late setting. The image below shows the increased radiation exposure to non-target tissue with X-Ray/IMRT when compared to protons.



In a study with stage III NSCLC patients, proton therapy is estimated to reduce 34% of radiation to the heart and 45% to the healthy lung when compared to IMRT (4).

The data in support of proton therapy and its unique advantages continue to grow. A study from M.D. Anderson demonstrated that proton therapy had better than expected median survivorship, lower local recurrence, and improved side effects compared to historical controls (5). Comparison across studies evaluating high dose X-Ray radiation and high dose proton radiation for locally advanced lung cancer suggests better treatment tolerability as well as outcomes with proton therapy (6,7).



It is based on these data that the CDH Proton Center has targeted intrathocaic tumors, particularly lung cancers as an area of tremendous benefit for our patients. Since its inception, our center has treated nearly

100 intrathoracic tumors including many challenging primary and recurrent lung cancers. As our multidisciplinary thoracic oncology program continues to grow, we look forward to providing this cutting edge treatment to many more patients.

We currently have two clinical trials available at the proton center for patients with lung cancer. These trials offer innovative ways to manage thoracic malignancies while collecting data for the benefit of future patients.

LUN005-12: A study for locally advanced lung cancer that uses higher doses of radiation per treatment combined with chemotherapy. This approach is believed to be more effective for tumor cell kill resulting in improved disease control.

UPCC 23309: The ability of protons to spare non-target organs often makes re-irradiation more safe and effective. This study is for recurrent tumors despite previous radiation arising from multiple body sites including the lung.

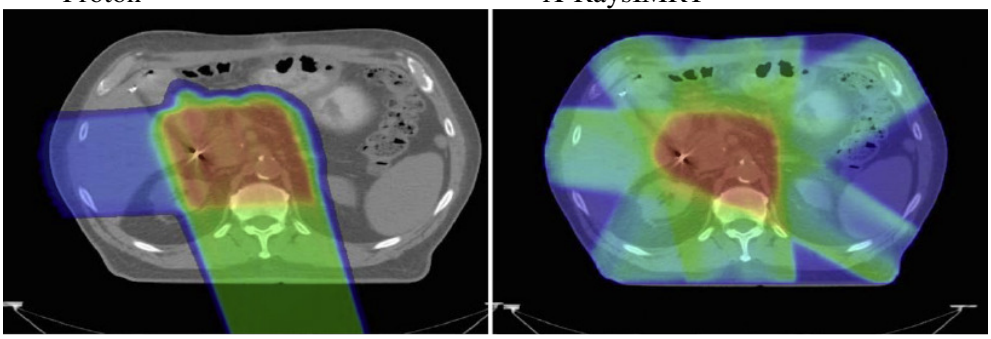
Gastrointestinal Malignancies

The CDH Proton Center is now offering treatment to patients with gastrointestinal (GI) malignancies such as primary tumors of the following disease sites: esophagus, pancreas, liver, rectum and anal canal. At the CDH Proton Center, patients have the option of being evaluated in a multidisciplinary setting. The GI tumor board meets weekly on Tuesdays and all patient cases are presented to an expert panel of physicians across disciplines including radiation oncology, medical oncology, surgical oncology, diagnostic radiology and pathology. All patients have the option of being seen the same day in clinic by the treating physicians to discuss treatment recommendations.

Proton therapy as an alternate modality of radiation allows for a more targeted approach compared to standard photon irradiation which allows adequate radiation dose to be delivered to the tumor while sparing dose to normal adjacent tissues (8). This improved dosing distribution allows for fewer acute toxicities allowing treatment to be more tolerable. It can also translate in to fewer long term side effects (9,10).

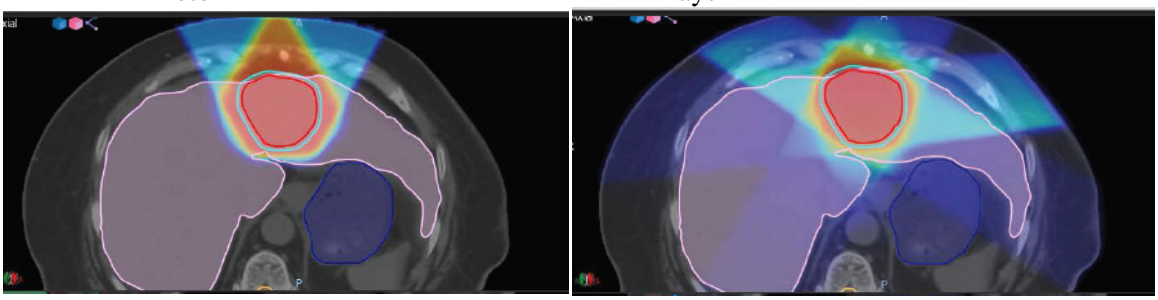
One example of the use of proton therapy in the treatment of GI malignancies is its use in pancreatic cancer. Treatment of pancreas cancer can be difficult due its natural aggressive pathophysiology, and also because of its location in the abdomen placing the radiation target in close proximity to other sensitive tissues. In most cases, surgery is the first method of treatment of pancreatic cancer to be considered and radiation is performed in the adjuvant setting with concurrent chemotherapy. The figure below demonstrates the improved dosing distribution of a proton therapy treatment plan on the left compared with a photon IMRT plan on the right 11). The red color-wash in the figures represent the high dose or prescription dose region while the yellow, green and blue color-wash indicate lower doses of radiation which covers more normal tissue in the photon IMRT plan on the right (12). In a recent publication, proton therapy demonstrated low rates of acute GI toxicities (13).

Proton X-RaysIMRT



Another example of proton therapy for GI malignancies is in the treatment of hepatocellular carcinomas (HCC). The figure below demonstrates the improved dosing distribution of a HCC treated with proton therapy on the left compared with IMRT on the right. This improved dosing distribution with proton therapy allows for less normal liver, kidney, stomach and bowel to be treated. Because of this, dose to the tumor can be escalated with proton therapy which can improve tumor control (14).

Proton X-RaysIMRT



Prostate cancer

Prostate cancer is the most common malignancy in men, and there is extensive experience in treating prostate cancer using proton beam therapy. The largest number of contacts to our center come from men with prostate cancer.
Our consultations for these men involve discussions regarding all treatment options, including surgery, other forms of radiation therapy, hormonal therapy and active surveillance.

Patient contacts (prostate cancer): 2477
Consultations: 1137
Patients treated with protons: 599
Active surveillance: 85
Other treatments: 450
From September, 2010, through December, 2013.

The vast majority (approximately 90%) of our patients who receive treatment are on clinical research studies, either through clinical trials or through registry studies.

PCG - GU002-10: A Phase III Prospective Randomized Trial of Standard-fractionation vs. Hypo-fractionation with Proton Radiation Therapy for Low Risk Adenocarcinoma of the Prostate.
ClinicalTrials.gov Identifier: NCT01230866

STRATIFY	**T stage** T1 vs T2a **PSA** <4 vs 4-10 **Cores +** 1-4 vs ≥5	**RANDOMIZE**	**Conformal proton radiation therapy** **Arm I:** 79.2 DRBE / 44 treatments 1.8 DRBE/day, 5 days/wk, 8-9 weeks **Arm II:** 38 DRBE / 5 treatments 7.6 DRBE/day, 5 days/wk, 1-2 weeks *1:2 randomization (twice as many patients randomized to Arm II)*	*This is a national, multi-center study. Thus far, more than 80% of the patients on this study have been treated at the CDH Proton Center. The patients on the short course treatment receive a higher dose each treatment, but the shorter course makes it much more convenient (and less expensive as well)*

PCG - GU003-10 Phase III Study of Mildly Hypo-fractionated Image Guided Proton Beam Radiation Therapy with or without Androgen Suppression for Intermediate Risk Adenocarcinoma of the Prostate
ClinicalTrials.gov Identifier: NCT01492972

PCG - GU004-11 Phase II / III Study of Dose-escalated External Beam Radiation Therapy With or Without Chemotherapy for High Risk Adenocarcinoma of the Prostate
ClinicalTrials.gov Identifier: NCT01603420

PCG-REG001-09 Evaluation Tracking Project: A Prospective Chart Review of Patients Treated with Proton Therapy
ClinicalTrials.gov Identifier: NCT01255748

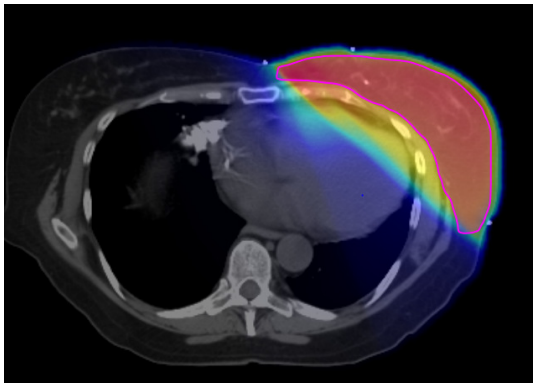
Breast Cancer

There is a large body of evidence suggesting an association between breast radiotherapy and a small, but significant risk of serious late toxicities including second malignancy and coronary artery disease. In recent years, advances in the detection and treatment of breast cancer have resulted in improved long-term outcomes. As a result, issues of survivorship are of paramount importance.

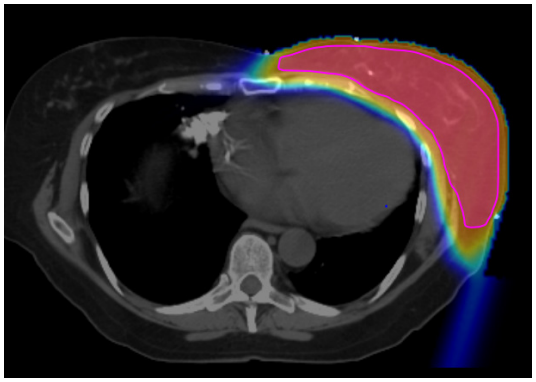
We are pleased to share with you that novel techniques for the treatment of breast cancer using proton beam therapy are now available at the Central DuPage Proton Center. Proton therapy has the potential to provide superior sparing of normal tissues adjacent to the breast or chest wall, including the heart, lung, and contralateral breast.

Shown below are radiation plans for the treatment of the breast and regional lymphatics in a two patients with Stage III breast cancer using standard x-rays (left) versus protons (right). With proton planning there is significantly less dose to the adjacent heart, lung, and contralateral breast. For both right and left-sided breast cancers, protons result in less unwanted radiation dose.

PHOTONS



PROTONS



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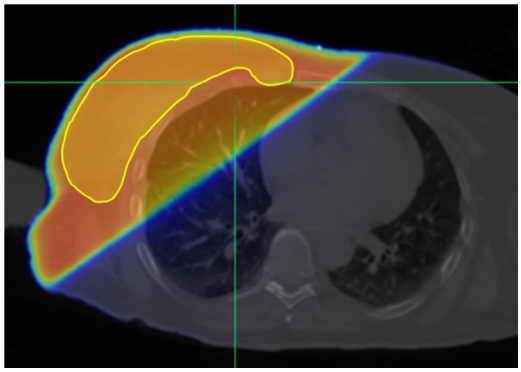

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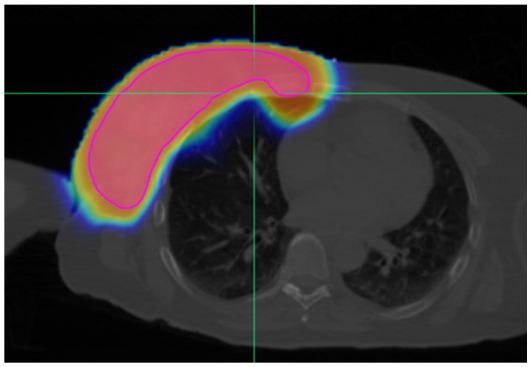

A Proton Collaborative Group (PCG) Phase II clinical trial is now open at the Central DuPage Proton Center to investigate the safety and efficacy of postoperative proton radiotherapy for complex locoregional irradiation in women with locally advanced breast cancers.

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