



 Abramson Cancer Center of the University of Pennsylvania

## Reduced Normal Tissue Toxicity With Proton Therapy

James Metz, MD

The Abramson Cancer Center of the University of Pennsylvania

Last Modified: June 29, 2006

Proton beams offer highly significant advantages over X-rays in the sparing of normal tissues. This is due to the physical characteristics of the proton beam compared to X-rays. X-rays are electromagnetic waves and are highly penetrating, and will deliver dose throughout any volume of tissue irradiated, regardless of thickness. Thus x-rays always deliver substantial doses of irradiation both anterior and posterior to any tumor volume. Furthermore even for the most energetic X-ray beams available for practice, the depth at which the maximum dose of radiation is delivered ( $D_{max}$ ) ranges from as little 0.5 cm to a maximum of 3 cm depending on the energy utilized. Because a tumor is almost always located deeper than these ranges, a higher dose is invariably delivered to the normal tissues anterior to the tumor, and the tumor is always treated in the region of the beam where the energy deposition is falling off. To some extent this can be overcome by bringing in beams from multiple directions, centered on the tumor, allowing the dose to sum within the tumor volume. However, since the beam travels throughout the entire thickness of the body, all normal tissues from the entrance area to the exit of the beam will be affected.

Unlike with X-rays, the absorbed dose of a proton beam increases very gradually with increasing depth and then suddenly rises to a peak at the end of a proton range. This is known as the Bragg Peak ( $D_{max}$  of a proton beam). A proton beam can be directed so that the Bragg Peak occurs precisely within the tumor volume, something that can almost never be done with X-rays. The dose around the tumor volume is much less than the tumor itself, thus sparing the normal tissue in this area. The dose immediately beyond the Bragg Peak of a proton beam is essentially, zero which allows for the sparing of all normal tissues beyond the tumor volume. Side effects, both acute and long-term, typically seen with X-ray therapy can thus be markedly reduced with proton beams due to the sparing normal tissues that are situated around the tumor. These considerations are directly related to the physical characteristics of the proton beam, and require no demonstration or study. However, data are available from clinical series that support them. It should be remembered that the available clinical data are somewhat limited, because clinical proton beam facilities are only now being developed.

A number of published studies have documented the clinical advantages of proton beams, and shown decreased normal tissue toxicity, compared to conventional photons (X-rays). Numerous sites within the body have been shown to be more effectively treated with proton beam therapy. By limiting the dose to normal structures, higher doses can safely be delivered to the tumor itself. This should result in higher local control and ultimately increased survival while minimizing side effects of therapy. The following is a review of the currently available literature comparing the toxicity of conventional photon and proton beams:

### Prostate Cancer

A significant proportion of patients treated in radiation oncology centers have prostate cancer. Side effects of treatment generally include gastrointestinal (GI) and genitourinary (GU) damage. Large numbers of patients experience urinary frequency and diarrhea during treatment, and long-term, may suffer impotence, incontinence, rectal fibrosis and bleeding, and extensive bowel fibrosis. These side effects may cause a reduction in the quality of life and result in delays of a typical radiation therapy treatment course. Tables 3 and 4 compare the acute and long-term complications of localized prostate cancer treated with protons, conventional X-rays, and radical prostatectomy, respectively. [Figure 4](#)

shows the reduction of normal tissue exposed to radiation with protons compared to photons (X-rays).

**Table 3. Acute complications associated with the treatment of prostate cancer**

Acute Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostatectomy
> Grade 2 GU toxicity (frequency, nocturia, dysuria)	0%	28%	N/A
≥ Grade 2 GI toxicity (diarrhea, rectal/abd pain)	0%	35%	N/A
Either GU or GI morbidity	0%	53%	N/A
Hospitalization	None	None	5-7 days
Absence from work	None	None	4-6 weeks
Death	0%	0%	0.3%
Pulmonary embolism/ DVT	0%	0%	2.6%
Myocardial infarction or arrhythmia's	0%	0%	1.4%
Wound Complications	None	None	1.3%
Lymphocele	None	None	0.6%
Surgical Rectal Injury	N/A	N/A	1.5%

**Table 4. Long-term complications associated with the treatment of prostate cancer**

Chronic Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostatectomy
Impotence	30%	60%	60%
Incontinence requiring a pad	< 1%	1.5%	32%
Bladder Neck contracture	0%	3%	8%
Chronic Cystitis	0.4%	5%	N/A
Grade 3 GU toxicity ● Severe frequency q 1 hr ● dysuria	0.3%	2%	36%
Grade 3 GI toxicity ● rectal bleeding requiring transfusion ● severe pain (>70 Gy)	0%	7%	N/A
Rectal stricture	0%	0.5%	N/A

**Lung Cancer**

Lung-cancer is the most common malignancy seen in men and women in the United States, and a very substantial source of all cancer mortality. A significant percentage of lung cancer patients are treated with radiation therapy at some point during the course of their disease. Since many of these patients have poor lung function due to years of smoking tobacco, preservation of functioning lung tissue is paramount. The destruction of lung tissue by conventional radiation techniques limits the delivery of

only measure of outcome is survival. Patients may be alive, but at considerable personal cost. This complication, xerostomia, is the sort of complication that is totally unavoidable with X-rays because of their through and through penetrating nature requiring us to treat both parotid glands even for well lateralized lesions, and which can be totally avoided with protons because of their lack of an "exit" dose. Given a choice of cure with or without xerostomia patients will make an obvious choice of protons over conventional X-rays.

**Table 7. Major side effects associated with treatment of head and neck cancer**

Side Effect	Protons N=200*	Conventional Radiotherapy (Photons) N=501**
Blindness (maxillary sinus tumors)	2%	15%
Xerostomia (Dry mouth)	< 5% (with protons alone)	100%
Dysphagia	12 %	100% 80% require liquid nutrition
Require PEG for nutrition	0%	30%

**Pediatric Tumors**

The treatment of pediatric tumors with proton therapy also provides a unique opportunity to significantly reduce the acute and long-term complications associated with conventional radiation therapy. The pediatric population is exquisitely sensitive to the effects of radiation therapy. Long-term sequelae including growth abnormalities, second malignancies, neurologic complications, cardiac and pulmonary toxicities, and infertility may all be reduced with the use of proton therapy. X-ray therapy causes effects on the hearts and lungs of pediatric patients, again due to the problem of "exit" dose. Proton beams should be able to entirely avoid these complications since the uninvolved normal structures can be totally avoided.

Well-recognized side effects of conventional photon irradiation of the brains of young children include neuropsychologic and intellectual deficits. The side effects vary directly with the volume of brain tissue irradiated and the dose of radiation delivered. By decreasing both the volume and dose of radiation to normal brain tissue through the use of protons, these side effects should be reduced. Table 8 outlines the reduced toxicity associated with proton therapy compared to conventional radiotherapy in pediatric patients.

**Table 8. Complications associated with cranial spinal irradiation in pediatrics**

Side Effect	Protons	Conventional Radiotherapy (Photons)
Restrictive Lung Disease	0%	60%
Reduced exercise capacity	0%	75%
Abnormal EKG's	0%	31%
Growth abnormality-Vertebral body receiving significant dose	20%	100%
IQ drop of 10 points at 6 yrs	1.6%	28.5%
Risk of IQ score < 90	15%	25%

Figures 5 and 6 show the difference in dose distribution between X-rays and protons for the treatment of the spinal axis in children with medulloblastoma. Figure 7 shows the difference in dose to the eye and optic nerves for treatment of a retro-orbital malignancy in a child.

PSA Level	Proton Therapy	Conformal x-ray therapy	Radical Prostatectomy
< 4	100%	91%	92%
4-10	89%	69%	83%
10-20	72%	62%	56%
>20	57%	38%	45%

Unfortunately, some patients experience a local recurrence of their cancer after treatment with radiation therapy. Only a minority of patients is curable after a recurrence because the normal tissues can not tolerate significant doses of additional radiation. Because protons can spare normal tissues, many patients that were not previously considered treatable again with X-rays may be treated with protons. This may further increase the cure rates in some specific malignancies.

Any site treated in the body with standard X-rays is a reasonable target for proton therapy. The physical characteristics of the proton beam will allow markedly decreased dose to normal structures. Not only can malignancies be treated, but also there is currently significant interest in the treatment of a number of benign diseases. This includes functionally abnormal areas that can be safely ablated by protons for diseases such as seizures, Parkinson's Disease, arteriovenous malformations, macular degeneration, and severe rheumatologic conditions. There is also interest in evaluating protons for the prevention of coronary artery restenosis after angioplasty and prevention of stenosis of peripheral vascular shunts that are created in patients requiring dialysis.

There are some preliminary data available on the treatment of macular degeneration. This is the leading cause of adult onset blindness in the United States. It is caused by the growth of blood vessels in the back of the eye, which are fragile and bleed. Current treatments include laser ablation, photodynamic therapy, standard X-ray therapy, and anti-angiogenic agents. Unfortunately, none of these treatments have been extraordinarily successful for most patients. Proton therapy offers the opportunity to safely deliver a much higher dose of radiation in a single treatment to the vessels in the back of the eye than is possible with standard X-rays. There are very encouraging preliminary studies from Loma Linda University Medical Center where over 200 patients have been treated with a single fraction of 14 Gy. The lesion control is 95% with either improvement in vision or no worsening of vision. Side effects are very mild and seen in <10% of patients.

[About OncoLink](#)
[Contact OncoLink](#)
[Privacy statement](#)
[Disclaimer](#)
[Link to OncoLink](#)
[Home](#)  
 For assistance please visit our [HELP](#) section  
 Copyright © 1994-2008 © Trustees of the University of Pennsylvania