Reduced Normal Tissue Toxicity with Proton Therapy

James Metz, MD
The Abramson Cancer Center of the University of Pennsylvania
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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 (Dmax) 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 (Dmax 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 potentially curative doses of radiation therapy. Tables 5 and 6 compare the acute and long-term complications of lung cancer patients treated with Protons versus conventional X-rays.

Table 5: Acute complications associated with the treatment of lung cancer

Acute Side Effects	Protons	Conventional Radiotherapy (Photons)
Nausea/Vomiting	0%	30%
Dyspnea	0%	16%
Esophagitis	<5%	31%
Fatigue	<5%	23%
> 5 lb. weight loss	0%	34%

Table 6: Long-term complications associated with the treatment of lung cancer

Chronic Side Effects	Protons	Conventional Radiotherapy (Photons)
Lung Fibrosis by CT scan	33%	85%
Normal Lung Destroyed	8%	29%
Lung injury $\geq$ Score 2	0%	62%
Decreased pulmonary function testing (VC, FEV_1, diffusion capacity)	0%	20%
Dyspnea	0%	32%
$\geq$ Grade 2 Esophagitis/Stricture	0%	10%
$\geq$ Grade 2 Pneumonitis	5%	15%
Cardiac Complications	0%	7%

The doses of radiation utilized in the treatment of esophageal cancer are similarly limited due to the normal tissues within the radiation treatment portal. The spinal cord, heart, and lungs can receive significant doses due to the location of the esophagus. Comparative treatment plans for esophageal cancer show advantages similar to those noted in tables 5 and 6 in using protons instead of conventional x-rays.

Head and Neck Cancer

The morbidity associated with the treatment of head and neck cancer with protons and conventional photons has been reviewed at various institutions. Specifically, cancers of the paranasal sinuses, tonsillar region, and nasopharynx have been evaluated. In each of these cancers, proton therapy should result in an improvement of local control with a reduction in the morbidity associated with conventional photon treatment. There has been a significant reduction in the rates of blindness seen in the treatment of paranasal sinus tumors as shown in Table 7. Also, comparative plans for the treatment of tonsillar and nasopharyngeal cancer revealed proton beam therapy can deliver higher doses of to the tumor volumes with significantly reduced radiation to the salivary glands and mandible than can photon beam irradiation. This results in a decreased incidence of xerostomia and radionecrosis of the mandible as demonstrated in Table 7.

It should be noted that essentially 100% of all patients treated for head and neck cancer with x-rays will experience severe xerostomia (dry mouth), which although it may not be life-threatening severely impairs quality of life. Many of these patients are for example unable to eat in a restaurant since they may require their food to be pureed or specially prepared for them to be able to eat it. It is these sorts of poor quality of life outcomes that are very inadequately measured in current cancer statistics where the 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 is 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.

Pancreatic Cancer

Comparative treatment planning performed at the Hospital of the University of Pennsylvania for the treatment of pancreatic cancer shows significant reductions in dose to normal structures. The tolerance of normal tissues has prevented effective dose escalation for this malignancy. Table 9 shows how protons can significantly reduce the dose to normal tissues and allow for dose escalation.

Table 9. Comparison between X-ray and proton doses for pancreatic cancer

Structure	X-ray Dose (Gy)	Proton Dose (Gy)	Dose Reduction	p-value
Spinal Cord	27	6	78%	.003
Liver	22	10	55%	.061
Right Kidney	14	8	43%	.059
Left Kidney	11	3	73%	.025

Considering the experience to date, proton therapy offers important advantages over X-rays. There is no question proton therapy results in a significant reduction in treatment related morbidity when compared to X-ray treatments. Because of this reduction in normal tissue toxicity, dose escalation studies are currently under investigation. This should further increase the local control, and ultimately survival, while minimizing treatment induced complications. Almost any site in the body may benefit from the use of protons compared to X-rays when normal tissue toxicity is analyzed.

Tumor Control with Proton Therapy

As more patients are treated with proton therapy, long term results on various sites of disease will be reported. When the same dose and fractionation regimens are used for X-rays and protons, there are similar cure rates. It is clear continued research is necessary to establish the optimum doses and fractionation of treatment for specific tumors using protons. Because protons can significantly reduce the side effects of treatment as noted above, studies on escalation of dose are ongoing. For many sites, increasing the dose of radiation therapy to the tumor may increase the ultimate cure rates. The following data are from sites already evaluated with proton therapy.

One of the most difficult areas to treat in the human body is a tumor that arises in the base of skull region. Damage to normal structures such as the brainstem, brain, cranial nerves, and optic chiasm can cause significant morbidity, thus limiting standard treatments. Surgical resection of this area is typically incomplete. Postoperative X-ray therapy achieves local control in only 35-40% of patients. It has been shown substantially higher doses of radiation therapy can be delivered with proton therapy. By delivering a median dose of 68.5 Gy with protons (typical X-ray dose= 54 Gy), significant improvements have been made in both local control and survival with these tumors. The 5-year local control rates for proton therapy are 91% for chondrosarcomas and 65% for chordomas. The 5 year overall survival rates range from 62%-88%. Proton therapy has become the standard of care for tumors of the skull base.

Uveal melanomas have historically resulted in loss of vision from the tumor or from the treatment, which consists of surgical removal of the eye. Over 2500 patients have been treated with proton therapy for uveal melanoma. The typical dose is 70 Gy over 5 treatments. The 5-year local control with protons is reported at 96%. The eye retention rate is 90% while the metastases free survival is 80%.

Loma Linda University Medical Center has treated over 1000 patients with prostate cancer using proton therapy. Using doses comparable to standard X-ray treatments they have shown significant reductions in side effects as noted above. They have currently devised dose escalation studies to find the maximum dose that can be safely delivered with protons to the prostate gland. Until the maximum dose is reached, final improvements in survival will not be known. However, the initial results reported based on PSA level with a very modest elevation of dose to 75 Gy are encouraging.

Table 10: Tumor control based on PSA at time of diagnosis

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 then 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.