Is Proton Beam Therapy more Effective than Intensity-Modulated Radiotherapy in Prostate Cancer Treatment?

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Abstract

Prostate cancer is the most common form of cancer found in American males. Breaking technological advances in prostate cancer treatment continue to develop to help fight this disease, one such is proton beam therapy. Proton beam therapy is theorized to spare even more healthy tissue than photon radiotherapy because it delivers a majority of its radiation during the Bragg peak. Since this technology is substantially costlier than any other form of radiation therapy, physicians are assessing its effectiveness and determining if it is worth the cost. Currently, there is no significant difference seen in patient quality of life between recipients of proton or photon therapy. This can possibly because of secondary neutrons that are generated when protons exit the nozzle. Pencil beam scanning, a recent advancement in proton therapy delivery, is theorized to make protons have much better treatment outcomes than photons and would eliminate the issue of secondary neutrons. More studies need to be conducted to determine if pencil beam scanning ensure better quality of life over photon therapy.

Introduction

Carcinoma of the prostate, more commonly known as prostate cancer, is a malignant tumor that develops on the prostate –a male organ that wraps around the urethra. Prostate cancer can occur in many different forms, such as carcinoid, small-cell tumors, and ductal carcinoma, however, these types are extremely rare and little is known about which treatment most effectively eliminates them. The vast majority of cases are adenocarcinoma, a tumor that originates in the gland cells. Prostatic adenocarcinoma is observed in over 95 percent of patients (National Cancer Institute 2014) and affects 15 percent of men predominantly above the age of 66, making it the most common cancer among American males (SEER 2014). Fortunately, prostate cancer tends to grow extremely slowly, and early treatment can often yield high survival rates. The most common treatment interventions for prostate cancer include surgery or radiation therapy. Within radiation therapy there are two methods, external beam radiation therapy (EBRT) and internal radiation therapy. The latter, also referred to as brachytherapy, involves the placement of radioactive pellets within the prostate gland that release a highly concentrated dose of radiation to eliminate the cancerous growth. External beam radiation therapy is employed by using a linear accelerator to accelerate electrons close to the speed of light and strike them against a metal plate. On impact, high-energy, ionizing photons are produced, which travel towards the targeted cancerous cells. The high amount of energy in the photons can irreparably damage vital structures in the cell such as DNA, RNA, or protein. Photons are able to directly harm the cancerous cells' DNA by energizing its electrons and pulling them out of their orbits. This produces free radicals, causing irreversible damage by altering the chemical structure of the nucleotides. Ionizing radiation can also delete, fragment, and translocate the nucleotides. Radiation can also indirectly harm DNA when photons collide with a cell's water molecules and energize its electrons. When a water molecule's excited electrons bounce out of their orbits it produces a hydroxyl ion ($OH-$). The hydroxyl ion is then able to extract a hydrogen atom from the deoxyribose part of the DNA, ruining the nucleotide's chemical configuration. Direct or indirect radiation damage to a cancerous cell's DNA is usually lethal. This is because the uncontrollable growth of the prostate cancer involves the mutation of the tumor suppressor gene TP53 (Wang et al. 1997). The protein that TP53 codes for is not only responsible for regulating the cell cycle, it is also responsible initiating DNA repair. As a result, cancerous cells are ineffective at repairing radiated DNA, and the cell's ability to proliferate is practically destroyed. Damaging 1000 nucleotides in DNA only takes one cobalt grey equivalent –the unit measure of radiation used during treatment.

Although external beam is an effective form of treatment, it also delivers radiation to surrounding healthy tissue. This is because before the advent of image guided treatment, physicians had to target the entire prostate to ensure that the entire tumor was radiated. Additionally, since the dose of radiation is gradually reduced as the beam passes through the patient, tissue directly in front of the tumor must be radiated to the prescribed dose. This leaves a track of radiation damage as the photons enter the body until it reaches the tumor. Furthermore, photons are massless particles and are not stopped or slowed down when they impact body tissue. This causes healthy tissue behind the tumor to receive radiation when photons travel past the tumor. Radiation to nearby healthy tissue often causes gastrointestinal and genitourinary toxicity, which can impair the patient's quality of life.

Advances in radiotherapy have greatly reduced these problems. The advent of three-dimensional conformal radiotherapy (3D-CRT) helps radiation oncologists treat prostate cancer more effectively. This sophisticated computer program creates a three-dimensional map to conform the radiation beam to the shape of the cancer and its surrounding normal tissues. Concentrating the beam more accurately to the cancerous area reduces the exposure of normal tissue to radiation, further reducing side effects after treatment. More recent advances in high precision targeting have led to intensity-modulated radiotherapy (IMRT), where

there is an even more effective manipulation of the radiation beam. The beam in IMRT is divided into multiple 'beamlets', aimed at the target from different directions. The 'beamlets'' shape and intensity are adjusted to avoid radiating nearby healthy tissue. By taking advantage of intensity-modulated 'beamlets', IMRT is able to deliver higher doses of radiation to the prostate. This arguably ensures greater eradication of cancerous cells while sparing even more healthy tissue than 3D-CRT. Additional advances include image-guided radiotherapy, which provides more accuracy to the targeted area in the event that patients or the organs inside them move during treatment.

Despite all the improvements in radiotherapy healthy tissue behind the tumor is still getting bombarded with radiation. Proton therapy is able to stop this. Proton therapy involves the therapeutic use of protons to radiate the DNA of cancerous cells. Protons are positively charged heavy particles, approximately 1800 times the mass of an electron. Therefore, protons need a particle accelerator to strip hydrogen atoms of their electrons, accelerate them to nearly the speed of light, and shoot them into tumors. Particle accelerators, either cyclotrons or synchrotrons, require an enormous amount of space, which makes the cost of a particle accelerator exceed 100 million dollars (National Association for Proton Therapy 2010). Upon entering the body, protons slow down due to their heavy weight and their attraction to the electrons in the body's cells. Consequently, physicians must program the particle accelerators to provide the protons with enough energy to reach the cancerous cells. After traveling the specified distance protons stop abruptly, depositing most of their energy at the targeted cells, sparing harmful radiation to the healthy cells behind the tumor. This biologic phenomenon, of depositing high dose and energy of the beam within the tumor while having minimal energy deposited beyond the tumor is known as the Bragg Peak Effect. During radiation treatment, physicians modify the Bragg peak and extend its distance to cover the entire depth of the tumor, ensuring that the entire tumor is radiated. Extending the distance of the Bragg Peak is accomplished by treating the tumor to different energies, which sends multiple sprays of protons to different depths of the tumor. This manipulation of the proton beam is called the Spread-Out Bragg Peak. Additionally, protons do not deposit much radiation when they enter the body. Taking advantage of the Bragg Peak Effect and the low entrance dose, proton therapy should theoretically achieve less exposure of radiation to normal tissue. This is believed to lead to higher prescribed doses, reduced complications of therapy, and greater efficacy in eradication of the tumor than any other form of radiotherapy.

Methods

Literature for this article was obtained using the Touro College Online library, in particular PubMed.
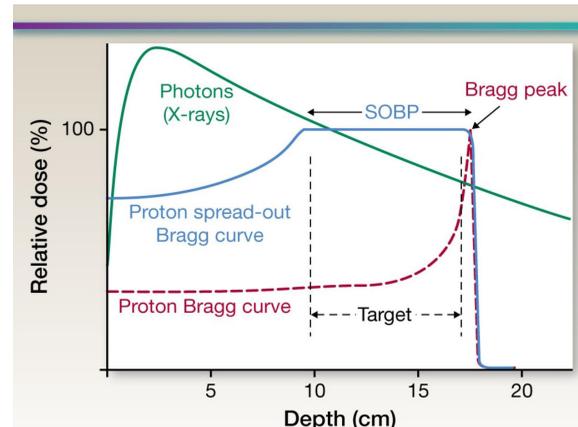
The graph compares the Bragg peaks of IMRT vs. Proton beam therapy. Protons, unlike photons, are clearly seen to delivery most of the radiation at the targeted cell.
(Mohan et al. 2013)

Discussion

Over the past decade, intensity-modulated radiotherapy has become the standard form of radiation treatment for prostate cancer, accounting for more than 80% of all radiotherapy (Nguyen 2011). Although IMRT is the most common method of radiation treatment, new forms of treatment are still emerging, most notably proton beam therapy. Proton therapy is currently being implemented at various cancer centers across America because of the excitement over the radiological advantages protons seem to offer. Even though there is a lot of enthusiasm over PBT, no factual evidence to prove protons are better than photons has been found. The lack of evidence in conjunction with the enormous cost of delivering the treatment is compelling physicians to determine if protons are more beneficial. To date there has been no clinical study that establishes that protons have a major advantage in cancer cure rates. This is because it is difficult to conduct cure rate trials, since such differences take many years to manifest. Therefore, the initial studies on proton therapy focus on treatment related toxicity and quality of life (Pearson et al. 2007). The organs most frequently affected by radiation toxicity after treatments are the bladder and rectum.

Dosimetric Analysis

A dosimetric analysis is the estimated measurement of ionizing radiation from the dose that is absorbed by nearby organs and is projected before treatment is delivered. This analysis helps physicians determine if there will be toxicity to nearby healthy tissue, which can downgrade the patient's quality of life. A study comparing the dosimetry of intensity-modulated radiotherapy and proton therapy was conducted to discover if protons spare more healthy tissue than photons on the bladder and rectum. Ten

patients were planned with both three dimensional conformal proton therapy and intensity-modulated radiotherapy. The prescribed dose for both treatments was 79.2 cobalt gray-equivalent (CGE) to the prostate gland. The study concluded that protons reduce the area of nearby healthy tissue that inadvertently receives low to medium, but not high doses of radiation. In contrast, intensity-modulated radiotherapy spreads more low and medium doses of radiation over a larger area of the pelvis (Table 1) (Trofimov et al. 2007). IMRT likely 'bathes' the pelvis with low to medium doses of radiation because it uses multiple 'beamlets' to target the tumor from different directions. As a result, there are more entry points into the patient's body as radiation is shot from the linear accelerator to the tumor.

More significant results were reported by a study from the University of Florida. The study also used 10 patients to compare proton beam therapy treatment with intensity-modulated radiotherapy, but with a prescribed dose of 78 CGE (Table 1) (Vargas et al. 2008). The difference in results between the study by Trofimov et al, in comparison to Vargas et al, can most probably be attributed to the difference in beam margins and arrangement. To be certain the cancerous growth was completely radiated, Trofimov et al, added a 10 mm margin around the clinical target volume, Vargas et al, only added 5 mm by 8 mm. By minimizing the margins, Vargas was able to better conform the beam to the tumor. When IMRT was delivered both studies used 7 beams, 52° apart from each other. However, for proton therapy, only Vargas et al optimized the beams. Beam angle optimization means physicians determine the 'beamlet' angles and intensities, so that the beams strike the tumor while sparing as much normal tissue as possible. Two steps are taken when determining the correct beam angle

and intensity. "First, the physicians through their experience and intuition decide the arrangement of the beams. Secondly, based on the orientation of the beams and the shape of the cancer, computer software optimizes the beam intensities." (Bertsimas et al. 2013).

A clinical investigation conducted by Chera et al, did not use beam angle optimization, but used the same prescribed dose and similar margins to Vargas et al (Table 1). Chera et al, concluded that the, "use of PBT significantly reduced the dose to normal tissues in the pelvis while maintaining adequate target coverage compared with IMRT" (Chera et al. 2009). Although the absolute difference between the two treatments was greater in the study by Chera et al, Vargas et al, managed to spare slightly more healthy tissue. One can conclude that beam margins play a more important role in limiting radiation from healthy tissue than beam arrangement.

In a recent study about the dosimetric impact on anatomical movements, Zhang et al, noted that the proton beam is affected by compensators that shape the beam at the end of the nozzle. As a result, protons experience more scatter than photons and minimizing the margins is extremely crucial. Although a dosimetric analysis was not the main focus of their study, Zhang et al reported that, "The proton therapy plan was better at sparing the rectum at doses of less than 50 Gy. However, above 50 Gy, IMRT was better at sparing the rectum" (Zhang et al. 2007). Clearly, all studies confirm that proton therapy reduces the amount of low to medium radiation unintentionally delivered to nearby healthy tissue. Yet, IMRT can sometimes yield better conformity to the target area in cases where high doses are delivered.

Table 1

Author	Dosimetric	Value Bladder	Rectum	Absolute Difference Bladder / Rectum
Trofimov	**30% CGE**	44.5%(IMRT) / 32.8%(PBT)	65.3%(IMRT) / 43.8%(PBT)	11.7% / 21.5%
	70% CGE	11.4%(IMRT) / 17.3%(PBT)	9.7%(IMRT) / 10.3%(PBT)	5.9% / 0.6%
Vargas	**30% CGE**	42.8%(IMRT) / 27.7%(PBT)	55.4%(IMRT) / 20.7%(PBT)	15.1% / 34.7%
	78% CGE	—	5%(IMRT) / 2.9%(PBT)	- / 2.1%
Chera	**30% CGE**	73.1%(IMRT) / 29.3%(PBT)	71.8%(IMRT) / 22.5%(PBT)	43.8% / 49.3%
	70% CGE	9.7%(IMRT) / 9.8%(PBT)	11.5%(IMRT) / 7.9%(PBT)	0.1% / 3.6%

Dosimetric Analysis Comparing IMRT Versus PBT (Pearlstein et. al 2013)

Toxicity and Quality of Life

Radiation poisoning of healthy tissue caused by protons can irritate the bladder, cause frequent urination, rectal bleeding, and sexual dysfunction. The question is, does toxicity to surrounding normal tissue result from the combined low and medium dose areas or the high dose area? A clinical investigation compared the rate of second cancers between IMRT and 3D-CRT. The study found that IMRT almost doubles the amount of second malignancies from 1% to 1.75%. This is because IMRT increases the amount of low dose radiation absorbed by surrounding healthy tissue (Hall et al. 2003). With this information it should follow that proton therapy, which substantially reduces low to medium unintentionally absorbed radiation should have significantly lower toxicity rates than IMRT.

A study was launched to discover if proton therapy causes less toxicity to nearby organs than intensity-modulated and three-dimensional conformal radiotherapy. There were 95 proton therapy patients, 153 IMRT patients, and 123 3D-CRT patients. Every patient's bowel and urinary functions were assessed 3, 12, and 24 months after treatment. The Expanded Prostate Cancer Index Composite (EPIC) was used to grade patients that received IMRT. Patients that received PBT or 3D-CRT were evaluated with the Prostate Cancer Symptom Indices, a similar scale to EPIC. In both tests scoring lower signifies lower quality of life. At three months following treatment, patients who received 3D-CRT or IMRT scored lower on the indices. They reported symptoms of urinary irritation, obstruction, incontinence, and a decrease in bowel quality of life. Proton therapy patients only reported minimal bowel and urinary morbidity. At 12 months all groups were equal on the indices when they reported decreased bowel quality of life. Only proton therapy patients reported a slight decrease in quality of urinary functions, such as irritation and obstruction, in comparison to the other groups. By 24 months all groups reported minor but clinically meaningful decrements in bowel and urinary functions quality of life. Proton therapy had a slight advantage for toxicities after 3 months and IMRT and 3D-CRT only had a slight advantage for urinary toxicities at 12 months. All groups had the same level of toxicity 24 months later. However, there are problems with this study. Firstly, each group received a slightly different dose to the prostate: 75.6 to 79.2 CGE for the IMRT patients, and 74.0 to 82.0 CGE for PBT patients. Different doses of radiation could have caused the different patterns of toxicity reported by the patients. Also, treatment was delivered according to each center's preferred practice and planning target volume margins were not explicitly mandated (Gray et al. 2013).

Another study on whether PBT can control the incidence of rectal toxicity only comprised of patients receiving the same dose, 74 CGE. Patients were followed up with after treatment to collect data on the toxicities at 1 month and once every 3 months for the first two years and once every 6 months thereafter. The rectal toxicities observed included anal pain at defecation and rectal bleeding. The bladder toxicities were urinary frequency, painful urination, and urinary retention. The patients were graded with the Common Toxicity Criteria 4.0, a scale created by the National Cancer Institute Grade 1 toxicity usually means minor toxicity. Grade 2 means symptoms requiring medications and grade 3 means symptoms requiring minor corrective surgery. The results revealed that PBT can achieve a low occurrence of grade 2 rectal toxicities and no major late toxicity was seen. (Nihei et al. 2011). The study by Nihei et al, takes care of some of the issues of the trial by Gray et al, that were mentioned earlier. Each patient had the same dose of radiation. In both studies a low amount of rectal toxicity is seen early on.

More significant results were found by a study conducted by Mendenhall et al. The authors used image-guided proton therapy to target the cancerous tissue. They discovered low amounts of grade 2 genitourinary and gastrointestinal toxicities (Mendenhall et al. 2012). These toxicity results do appear more favorable than results commonly reported with IMRT. There was a high incidence of grade 1 and 2, and some patients experienced grade 3 toxicity. (Valeriani et al. 2014). Even more surprising was the fact that Valeriani et al, used image-guided IMRT and the prescribed dose was much lower, 68 CGE. The image guided radiation and the low amount of radiation should have curtailed the amount of toxicity that was reported.

Only one study reported overall worse gastrointestinal toxicity rates for protons than photons. The study used data from Surveillance, Epidemiology, and End Results (SEER), a Medicare linked database. Sheets et al, analyzed patient reported outcomes based on billing claims for diagnoses and procedures from sixteen cancer registries. There were 684 patients treated with proton therapy and 6666 with IMRT. The authors observed that, "proton therapy–treated patients were more likely to receive a diagnosis of gastrointestinal morbidity and undergo gastrointestinal procedures" (Sheets et al. 2012). However, this investigation did not report information on the prescribed dose and target margins. If the dose and margins differed between the two groups it could have caused a difference in toxicity rates. Another issue with this study is that Sheets et al, used claims for colonoscopy to measure gastrointestinal toxicity rates. This would be an imprecise surrogate for any population. This is the same population that might also be more concerned about colonoscopy screening, and therefore would receive more gastrointestinal procedures. This study should not be used to relay any important morbidity information to inquiring patients. The few studies on quality of life have only shown modest advantages associated with proton therapy in comparison with other forms of radiotherapy.

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Problems with Scatter Beam Proton Therapy

Theoretically, protons should be the superior form of radiation treatment because of the Bragg Peak Effect. However, this phenomenon also makes the protons extremely sensitive to uncertainties during treatment. If a physician is unsure how deeply situated the tumor is, protons will not destroy the cancerous cells if it is not given even energy to reach that area. In contrast, photons continue to deposit a substantial amount of radiation as they transverse the entire body. As a result, physicians end up programming the Spread-Out Bragg Peak to extend deeper into the body, irradiating nearby healthy tissue. Additionally, the Spread-Out Bragg Peak requires multiple shots of protons to be passed through the body to completely radiate the entire depth of the tumor. This causes the tissue in the front of the prostate to be exposed to many doses of radiation. Additional concerns have recently been raised that organ toxicity can also be a result of secondary neutrons. Secondary neutrons are created when protons collide with the collimator –a metal piece that shapes the beam. The collimator is made out of brass and when struck by protons it sends off secondary neutrons. Low secondary neutron radiation can cause patients receiving treatment to develop a high chance for contracting second malignancies (Brenner et al. 2008). These neutrons could be stopping PBT from having better toxicity results. Although there are simple fixes to reduce the amount of neutrons, such as using a material with a low mass number, these techniques do not substantially curtail the amount of neutrons (Gould 2009).

Pencil Beam Scanning

Recently, a newer method of delivery has been added to proton therapy. The older method, Scatter beam uses thick beams of passively scattered protons. The beams are shaped through slits in metal plates that form a relatively large beam as it exits the particle accelerator. The latest improvement to proton beam therapy is pencil beam scanning. Also known as spot scanning, this method is more accurate version of proton therapy. Pencil beam employs an extremely narrow beam that is brushed from side to side, 'painting' the dose on the tumor spot by spot. Because no apertures are needed, the protons do not collide with any metal and secondary neutrons are not produced with the collimator. The beam targets each spot on the tumor with a specific dose of radiation. Pencil beam scanning can even adjust the Spread-out Bragg Peak for every individual cancerous cell. "Scattered beam and pencil beam can be compared to a painter spraying with a spray can versus an airbrush. Instead of needing a stencil to master the shape, the proton beam is made ultra fine to define the contours and landscape of a tumor" (MD Anderson 2009). With pencil beam protons are turned into an intensity-modulated type of treatment. This is projected to give protons more conformation to the cancer and its surrounding healthy tissues. Recently, a small number of cancer centers that deliver proton therapy introduced

this new technology (Weisenbaugh 2014). To date, it is premature to determine if pencil beam is the most optimal method to use in the fight against prostate cancer. Only one study concluded that there is no toxicity or quality of life differences between passively scattered and pencil beam. The clinical investigation was comprised of 226 men who received passively scattered proton therapy and 65 men who received pencil beam proton therapy. Both groups reported similar gastrointestinal toxicity results, grade 2, throughout the 24-month trial. Genitourinary toxicity was also grade 2 and occurred mostly in the first 12 months following treatment. Yet, the authors acknowledged that, "Future comparative analyses between spot-scanning and passively scattered are warranted in a larger cohort" (Pugh et al. 2013).

Conclusion

Proton beam therapy can cure prostatic adenocarcinoma as efficiently as IMRT. If proton therapy would not be extremely expensive this therapy would be less controversial. Protons would have been regarded as another type of treatment used to eradicate cancerous cells. However, because proton therapy is considerably more expensive it draws criticism to the fact that it only has a meager benefit over IMRT. PBT is slightly more effective in curtailing the amount of low to medium dose of radiation to the nearby organs. However, this only translates into a modest advantage in early toxicity over intensity-modulated radiotherapy. Currently, there is no clinical evidence that proves scatter beam proton therapy is a significantly better form of treatment than IMRT. However, since there are limited centers that deliver proton therapy and relatively few patients that received it, more studies need to be conducted to solidify this claim. Although scatter beam might not be so advantageous in comparison to intensity-modulated radiotherapy, pencil beam proton therapy is theorized to turn protons into the ultimate form of treatment. More clinical trials need to be conducted to find out if pencil beam technology gives proton therapy the edge in the battle against prostate cancer.

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