Spring 2017

Radiation Therapy Medical Physics Review – Delivery, Interactions, Safety, Feasibility, and Head to Head Comparisons of the Leading Radiation Therapy Techniques

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Abstract

Radiation therapy uses high energy radiation to kill cancer cells[1]. Radiation therapy for cancer treatment can take the form of photon therapy (using x-rays and gamma rays), or charged particle therapy including proton therapy and electron therapy. Within these categories, numerous methods of delivery have been developed. For example, a certain type of radiation can be administered by a machine outside of the body, called external-beam radiation therapy, or by a "seed" placed inside of the body near cancer cells, called internal radiation therapy or brachytherapy[2]. Approximately half of all cancer patients receive radiation therapy, and the form of radiation treatment depends on the type of tumor, location of the tumor, available resources, and characteristics of the individual receiving treatment[3]. In the current paper, we discuss and review the various forms of radiation therapy, the physics behind these treatments, the effectiveness of each treatment type compared with the others, the latest research on radiation therapy treatment, and future research directions. We found that proton therapy is the most promising and effective form of radiation therapy, with photon methods such as intensity modulated radiation therapy, 3D-conformal radiation therapy, image guided radiation therapy, and volumetric modulated radiation therapy also showing very good comparative performance.

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1. Background

1.1 How does radiation therapy kill cancer cells?

The type of radiation that we are discussing in the context of radiation used for cancer treatment is called ionizing radiation. This is because it forms electrically charged particles in the cells of the tissues that it comes in contact with. It does this by removing electrons from the atoms and molecules in the tissues that it passes through[4]. This process kills cancer cells because it damages their DNA. The radiation can both damage the DNA directly by coming in contact with the cells or by creating free radicals (unstable molecules that can build up in cells and cause damage to DNA, lipids, and proteins) within the cells that then go on to damage the cancer cell DNA[1,2]. Ultimately, cancer cells with damaged DNA stop dividing and die. After death, these cells are broken down naturally in the body and eliminated[2]. As a result, the cancer has been combated and hopefully eliminated.

The overwhelming issue with this process is that radiation therapy does not exclusively attack cancer cells. It can just as effectively damage normal cells. This leads to serious side effects, which can be both acute (such as nausea and vomiting) and chronic (such as second cancers), damage to important organs, and other defects such as cardiac failure, endocrine deficiencies, or deafness. As a result, the amount of radiation that normal tissue can receive without significant damage is known for all parts of the body. For example, reproductive organs are more sensitive to radiation than bones[2]. Attention to sensitivity of nearby tissues, along with overall attention to reducing excess dose to healthy tissues, is central to treatment planning and decisions about which type of therapy is the best for a given case and how it should be administered[2].

1.2 Treatment Process Overview

Creating a radiation therapy plan begins with a simulation. The tumor is imaged using one of four main types of scans: computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET), or ultrasound scans. A simulation is run using these images to plan the radiation therapy so that the target area is precisely located and well-marked. Because the initial treatment and all subsequent treatment sessions are based off of the simulation, physicists and radiation oncologists go to great lengths to ensure that the patient is in the exact same position every day (relative to the machine administering the treatment). This includes the use and personalized construction of body molds, face masks, and skin markings to regulate patient positioning. After imaging and simulation the treatment plan is finalized and the treatment region, total radiation dose delivered to the tumor, dose allowance for neighboring healthy tissues, and safest angles and pathways to the tumor are determined and confirmed[2]. Again, central to the analysis of the tumor and the consideration of all of these factors is the decision of which type of therapy is best, and this decision relies on the physics of the particles and rays in question and the physics of the delivery tactics of the

machines. The exact treatment plan is developed using radiation therapy specific computer programs.

The radiation dose for cancer treatment is measured in grays (Gy). This is a measure of the amount of radiation energy absorbed by one kilogram of human tissue. The dose needed depends on the size, location, and specific type of cancer cell[2].

Within each treatment plan, normal tissue surrounding the tumor is irradiated. Part of this exposure is simply due to the limitations in specificity of the technology or difficult tumor placement. However, a limited amount of radiation to nearby neighboring tissues is always calculated into the treatment plan to take into account body movement due to breathing and general organ movement, and also to reduce the likelihood of tumor regrowth due to cells that have spread to the normal tissue adjacent to the tumor site. The latter is called microscopic local spread. Essentially, the goal is to irradiate a small portion of neighboring tissue to ensure that the entirety of the tumor has been eliminated[2].

2. Types of Radiation Therapy

As stated previously, there are two main types of radiation therapy: photon therapy and charged particle therapy. Photon therapy is comprised mainly of gamma rays and x-rays while charged particle therapy usually takes the form of proton therapy and electron therapy. Within each of these branches, there are many ways to administer these therapies. The differences between the behaviors of each type of therapy are crucially important to recognize and understand. The type of radiation therapy prescribed depends on many factors including the size of the cancer, the type of cancer, the cancer's location in the body, proximity to important organs and tissues sensitive to radiation, how deep in the body the tumor is, and patient considerations such as age, health, pregnancy, and medical history[2]. Much of the debate in radiation therapy is focused on proton therapy versus traditional photon therapy. However, the exact effectiveness of each type is heavily determined by the administration method in addition to the pure nature of each particle. The most important knowledge when deciding which type of radiation therapy to use is a deep understanding of the physics underlying each reaction, method of delivery, and tumor characteristic.

The focus of this review is on external-beam radiation therapy. Most forms of external-beam radiation therapy are delivered using a linear accelerator. This machine uses electricity to form an extremely fast stream of subatomic particles. The linear accelerator uses microwave energy to accelerate electrons to speeds nearly the speed of light over a short distance. In the case of photon therapy, when the electrons reach maximum speed they collide with a tungsten target. This subsequently releases photon rays which are directed to the area of interest[5]. This creates high energy radiation that is given to patients daily for several weeks of treatment. The most effective linear accelerators can rotate to any angle around the patient so that the beam can be directed in the most favorable angles. Here, we dive into an in depth introduction to the most common forms of external-beam radiation therapy.

2.1 Photon Therapy – Overview

When a beam of x-rays or ϒ-rays passes through a medium, the radiation is delivered through energy transfer to the medium. This transfer begins with the ejection of electrons from atoms in the absorber, in this case the human body. These expelled electrons transfer their energy by creating ionization within the absorber and exciting atoms in their paths. The energy that results from this process deposits into the cells of the body and destroys their ability to reproduce[15]. This is different than in charged particle therapy, where the charged particles such as electrons and protons fall into the category of directly ionizing radiation where these particles have enough energy to produce radiation by collision. The radiation by uncharged particles, such as these photons, falls into the category of indirectly ionizing radiation because they act by releasing directly ionizing particles from the absorber material when they pass through it[1,15].

The photon beam is characterized in a variety of ways. First, we consider the fluence, which we can understand as the robustness of the beam. The fluence (ϕ) of photons is the number of photons (dN) that enter an imaginary sphere of cross sectional area da given by

(1) $$\Phi = \frac{dN}{da}$$

This can be adapted to represent the fluence rate or flux density (the fluence per unit time), the energy fluence (the sum of the energies of all of the photons that enter a sphere of cross-sectional area da), and the energy fluence rate or intensity (the energy fluence per unit time)[15].

Another important factor to consider is photon beam attenuation. By passing a beam of photons through an absorber of variable thickness and detecting the number of primary (non-scattered and not-yet-interacting) photons at various depths, the beam attenuation was experimentally measured. It was found that the reduction in the number of primary photons (dN) is proportional to the number of incident photons (N) and the thickness of the absorber (dx). This is represented by

(2) $$dN = -\mu N dx$$

where μ is the attenuation coefficient. This coefficient depends on the energy of the photons and the nature of the material. There is a minus sign in the equation to show that the number of photons decreases as the absorber thickness increases. This can also be adjusted to be in terms of intensity where $dI=-\mu I dx$. When discussing the attenuation coefficient, the half-value layer is often mentioned. This is a sort of half-life equivalent term which is defined as the thickness of an absorber that is required to attenuate the beam intensity to half of its original value[15]. The attenuation of a photon beam is caused by four types of reactions: coherent

scattering, the photoelectric effect, the Compton effect, and pair production. Each of these have their own attenuation coefficient where

(3) $\mu=\sigma_{coherent} + \tau + \sigma_{Compton} + \pi$

and each of these components is the attenuation coefficient for the reactions listed above, respectively.

It is three of these processes - the photoelectric effect, the Compton effect, and pair production - that are the primary processes by which the ionizing photons interact with atoms in the absorber to produce the high speed electrons that create the therapeutic radiation. Coherent scattering, which was mentioned above, is left out of this discussion. That is because coherent scattering is an interaction with an electromagnetic wave passing near the electron and setting it into oscillation. This electron radiates energy in the same frequency as the incident electromagnetic wave, so the scattered x-rays have the same wavelength as the incident beam and no energy is changed and no energy is absorbed by the medium (figure 1A)[15]. The other three processes, however, are crucial to an understanding of photon therapy.

The photoelectric effect is a process where a photon encounters an atom and ejects one of the orbital electrons from the atom. When this happens, the entire energy of the photon is absorbed by the atom and then transferred to the atomic electron. The ejection of this electron creates an empty space in the shell which leaves the atom in an excited state. The angle in which the electrons are ejected depends on the photon energy. For photons with lower energies, the photoelectron is emitted at an angle around 90 degrees relative to the direction of the incident photon. As the energy of the photon increases, the angle of photoelectron emission is directed in a more forward direction[15]. Because the incident photon is absorbed in the process and an electron is ejected, the photoelectric effect is both a reason for the attenuation of photons as the beam passes through material and an explanation for the therapeutic effects of photon radiation. This process is pictured in figure 1B.

The second process that characterizes photon radiation is the Compton effect. Here, the photon interacts with an atomic electron as though it were a free electron. This means that for this process to occur, the binding energy of the electron must be much less than the energy of the incident photon. The photon does not lose all of its energy and the electron receives some of the energy from the photon. The electron is emitted at an angle Θ and the photon is scattered through an angle of ϕ (figure 1C). The process is thought of as a collision between two particles and from this the following relationships can be derived:

(4) $$E = h\nu_0 \frac{\alpha(1-\cos\phi)}{1+\alpha(1-\cos\phi)}$$

(5) $$h\nu' = h\nu_0 \frac{1}{1+\alpha(1-\cos\phi)}$$

(6) $$\cos\theta = (1+\alpha)\tan\phi/2$$

where hv_0 is the energy of the incident photon, hv' is the energy of the scattered proton, and E is the energy of the electron. $\alpha = hv_0/m_0c^2$ where m_0c^2 is the rest energy of the electron[15]. Overall, the Compton effect occurs when the energy of the incident photon is much greater than the electron binding energy whereas the photoelectric effect is most probable when the energy of the photon is equal to (or slightly greater than) the binding energy of the electron.

The final process that produces high speed electrons and determines the attenuation of photons is pair production. If the energy of the photon is greater than 1.02 MeV, the photon is able to interact with the absorber material through pair production. Here, the photon gives up all of its energy when it interacts with the electromagnetic field of an atomic nucleus. This yields a negative electron and a positive electron. This is where the 1.02 MeV number comes from – the rest mass energy of the electron is 0.51 MeV so 1.02 MeV is required to create this pair. This process is an example of an interaction in which energy is converted into mass. Because the photon must interact with the electromagnetic field of the nucleus, the probability of pair production taking place increases with atomic number[15].

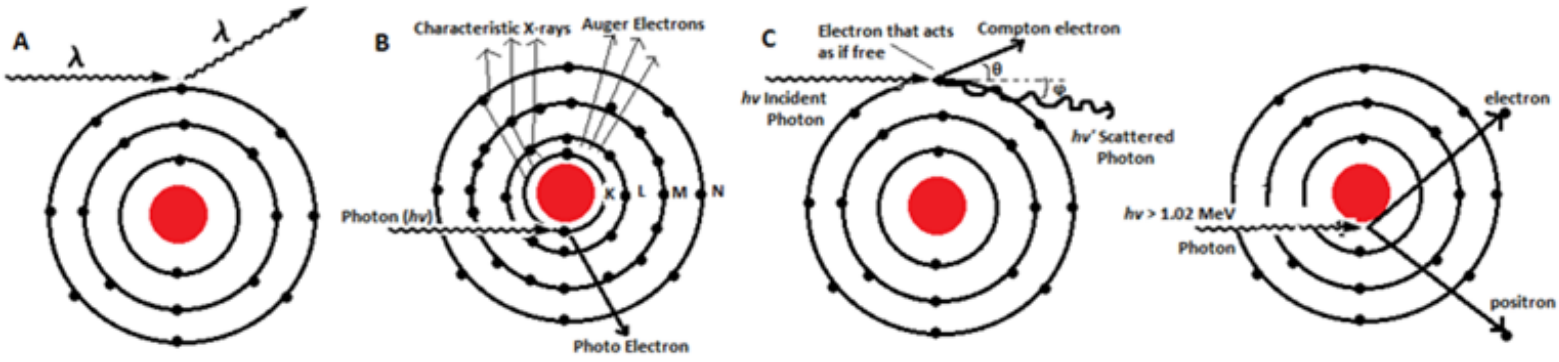

Figure 1: Shematic illustrations of the three processes that can occur in photon radiation therapy. Image A illustrates coherent scattering, image B illustrates the photoelectric effect, image C illustrates the Compton effect, and image D illustrates pair production.

While the energy of the incident photon dictates which sort of radiological process takes place, it also dictates the quality of the beam. Beam quality is the sharpness and homogeneity of the beam. Because high energy photons direct electrons in the forward direction after each type of collision, with increasing beam energy comes increasing beam quality and lateral conformity. There is less radial scattering with high energy beams.

To summarize the important features of this discussion and develop an overarching understanding of photon therapy, we must discuss the Bragg peak. This peak traces the path of the photon with respect to energy released and highlights what is called the entrance dose and exit dose, two very important features of photon therapy. The orange curve, representing X-ray delivery in human tissue, of the Bragg peak in figure 2B has a shape that is clearly significantly different in appearance than the respective proton curve (blue). The X-ray curve (which for these purposes, is representative of all forms of photon therapy) is characterized by

an entrance dose with a very high dose of radiation delivered to anterior tissues followed by an exponentially decreasing dose through the target tumor location and then an exit dose far more significant than that of the proton curve. When photons penetrate a material they consistently deliver radiation until the beam runs out of energy and the majority of photons have been eliminated through the attenuation reactions discussed. This results in the greatest amount of radiation being released at the surface and in shallow tissue (the entrance dose) and a significant amount of radiation penetrating past the target tumor and into healthy tissue behind the cancer (the exit dose). Instead of the depth dependent controlled dose that will be analyzed in our proton therapy discussion, we see a messy Bragg peak with radiation seeming to leak into a significant amount of healthy tissue. Entrance and exit doses to healthy tissues are not desired and can lead to a variety of negative side effects which will be discussed.

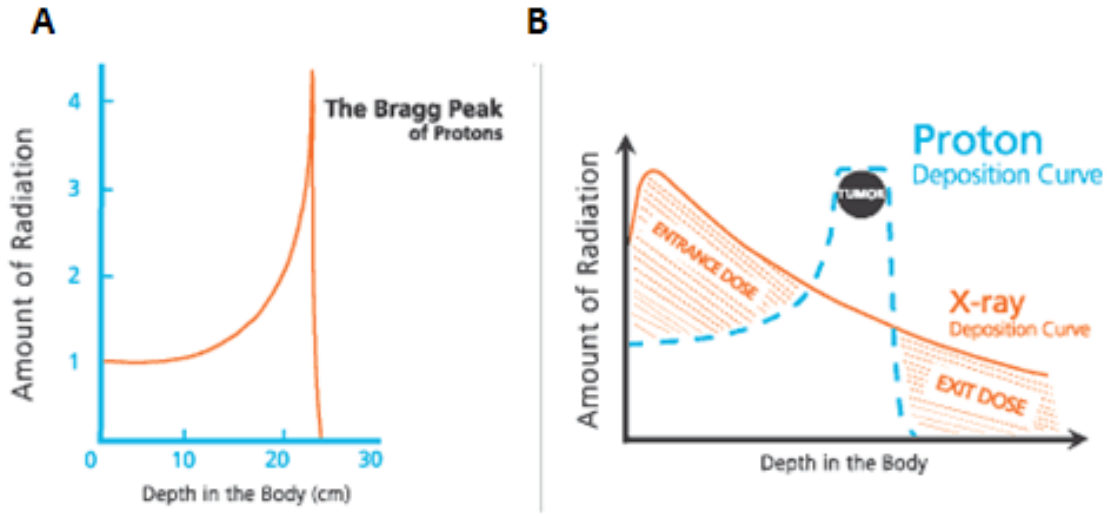

Figure 2: Three Bragg peaks on two plots. Image A depicts the path of a single proton as it enters the body and delivers the overwhelming majority of its energy at a single, controllable, point. Image B displays a head-to-head comparison between the deposition curve for a single proton (blue) and a single X-ray (orange). Figures adapted from the Loma Linda University Cancer Center, 2017.

The Bragg peak, with photon therapy's exit and entrance doses highlighted, is the first indication that photon therapy has some significant weaknesses. Over the years, however, a variety of creative and effective novel forms of photon dose delivery have been created. These address each of the issues inherent to photon therapy and make improvements. Each new technique builds off of the holes in the previous technique. The overall collection of photon therapy treatment methods has been able to side step some of photon therapy's disadvantages in a more cost effective way[12]. The evolution of photon therapy strategies and each one's strengths and weaknesses is presented below.

2.11. Two-Dimensional Photon Therapy (Conventional Radiation Therapy)

Conventional Radiation Therapy is the most basic form of photon therapy. Each of the following methods have addressed issues and oversimplifications in this treatment strategy and improved upon this design. 2D-PT uses X-ray films to determine how to position the radiation beams in order to target the tumor. A fluoroscopic simulator machine is used to plan the treatments where the bones on the X-ray image are used as landmarks to pinpoint the best way to position the radiation beams in order to eliminate the tumor. 2D therapy uses two unadjusted beams directed at the target from opposite sides[11]. In 2D treatment of breast cancer, for example, the breast is shaped such that the armpit and skin under the breast become "hot" during treatment where they receive a greater dose than the rest of the tissues that the photon beams pass through. This leads to skin burns[2]. While side effects like this with both short and long term implications are concerning, a potential benefit to conventional radiotherapy is that the treatment plan can be completed very quickly and patients are able to get their treatment as soon as necessary. For that reason, this technique is most commonly reserved for when urgent treatments are required[11].

2.12 3D Conformal Radiation Therapy (3D-CRT)

In 3D-CRT, the greater number of beams and greater variation in delivery angle allows the photon rays to be delivered from many different entry points, giving a lower dose to each section of tissue on the outer parts of the body and collecting each beam of radiation to deliver a strong dose to the tumor. Photon therapy is currently the most common form of radiation therapy. One of the most common types of photon therapy is 3D-CRT. This form of treatment uses sophisticated computer programming to create a 3-dimensional picture of the tumor[2]. First, a CT scan is conducted. This is translated to the treatment planning software that creates the 3D image of the tumor so that it is easier to determine the best beam direction and intensity for treatment. This allows for a more directed photon beam so that normal tissue can be spared. Because it uses several beams from different angles, 3D-CRT is able to improve upon the treatment delivered by 2D conventional photon therapy. The multi-angle optimized approach of the 3D-CRT allows side effects such as the skin burns and potential dangers in 2D conventional therapy to be avoided and leads to dose optimization in the tumor[5]. Of the most basic photon therapy techniques, 3D-CRT is favorable because it allows for treatment of tumors in sensitive areas such as the head and neck which are close to vital organs. It can safely treat these areas because of 3D-CRT's spatial localization and ability to enter from precise angles.

2.13 Intensity-Modulated Radiation Therapy (IMRT)

The key piece to IMRT treatment is the incredibly precise collimators integrated into the system. IMRT uses hundreds of tiny collimator pieces to shape the entry pathway for the photon beam. The machines administering this treatment have special collimator features built in that are able to individualize the collimator shape for each patient using layers of tiny nail shaped lead or tungsten pieces[6]. A special benefit to this setup is that the collimators can move during treatment, allowing for modulation of the intensity of radiation beams within a single session. With this, the result is a treatment plan that allows different areas of the tumor or of

nearby tissue to receive different doses of radiation. The collimators form many different shapes, typically 50 or more, during the course of a radiation treatment[11]. The strength of this feature and of the 3D features first introduced in 3D-CRT are illustrated in figure 3. Image 3A shows the treatment plan for 2D conventional radiation therapy for a patient with prostate cancer. A broad region is blocked out (yellow line) and multiple overlapping beams are used to create this brick shaped region of high dose delivery[6]. While this plan is fast and easy, an unwanted result is the irradiation of large volumes of the small bowel, rectum, and bladder. Image 3B shows a new treatment plan with the introduction of CT scanning and 3D-CRT. Here they were able to reconstruct the target volume three dimensionally and shape the radiation beams to fit the volume and begin to shield normal tissues. While they achieved improved spatial dose distribution, they were still unable to shield healthy surrounding tissues from exposure. Finally, image 3C displays an IMRT treatment plan. Here we see the most advanced plan that uses specific collimators to get an exact shape and takes advantage of non-uniform intensity of radiation beams. This is where the intensity modulation, one of the greatest novelties and strengths of IMRT, comes into play. In this image, strength of the dose in number of particles per second is represented by the color variation in the treatment plan image. The varied intensity is achieved by using many beams and subdividing each beam into hundreds of "beamlets" that each have an individual intensity level[6]. This means that multiple beams are arranged at various angles and then each of these beams is broken into hundreds of beamlets. All of this variation in this complicated dose delivery system comes together to create the incredibly complex treatment pattern in figure 3C.

An interesting aspect of the treatment planning for IMRT is that it is created in reverse. The oncologist and physicists select the radiation doses that they would like to deliver to each area of the tumor and adjacent tissue, feed this distribution into a computer program, and then this program calculates the required number of beams and the angle of delivery for the treatment plan[7]. This allows more effective treatment because the areas that need high dose are able to get increased radiation, while also allowing for a safer treatment process because sensitive healthy tissues are exposed to a significantly reduced dose. This delivery method improves upon some of the advances made between 3D-CRT and 2D radiation therapy by further reducing several common side effects and delivering a more localized beam and treatment plan. It is also particularly useful when the tumor has a concave or complex shape[6]. However, with IMRT, some studies alternatively suggest that a larger volume of normal tissue is exposed to radiation overall compared with 3D-CRT. IMRT also has the potential to be more risky than 3D-CRT. It is a complex treatment process that relies on extremely precise plots of direction, adjustment, and intensity of radiation beams. Because of this, great care must be taken to ensure absolute precision in patient placement because small movements on the millimeter scale as a result of breathing, heartbeat, or imprecise placement can distort the radiation pattern. Experimental comparisons between the two, as will be discussed, are critical to the development of an understanding of when each method is the superior choice given a specific cancer type or tumor location.

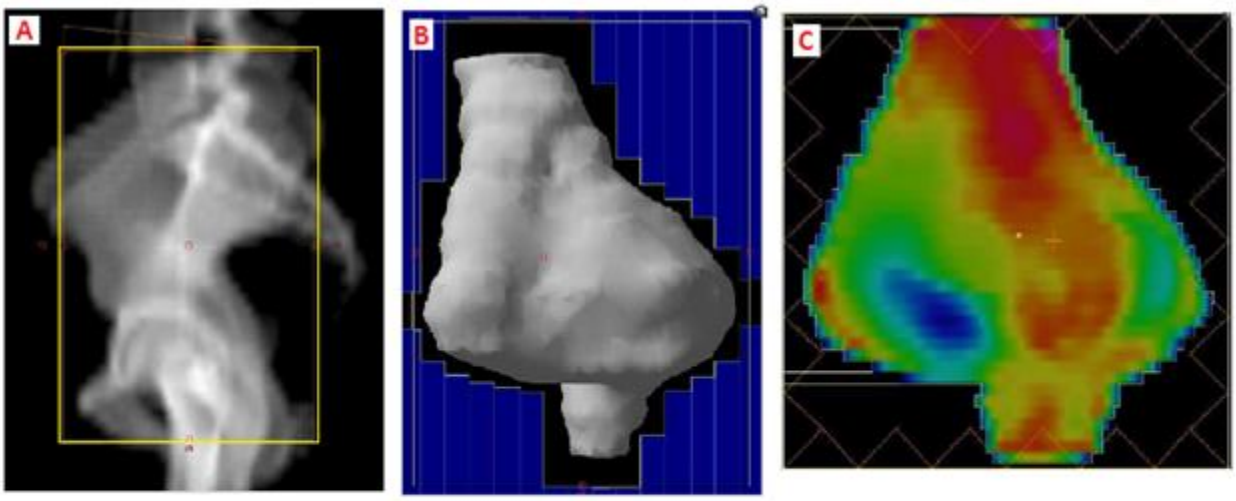

Figure 3: Treatment plans for the same prostate cancer tumor using three different photon radiation therapy treatment systems. Image A is the treatment plan using 2D Conventional radiotherapy. The yellow box represents the region of high dose delivery. Image B is the treatment plan using 3D-CRT where a 3D image of the tumor is created for the plan. Image C represents the plan created for IMRT treatment. The variation in color represents variation in intensity of dose delivered (particles per second) with red representing the region of highest dose. Images adapted from Taylor et al. 2004.

2.14 Image Guided Radiation Therapy (IGRT)

In IGRT, throughout the course of treatment, imaging scans from either CT, MRI, or PET are repeatedly collected. Computer systems collect these scans and process them to identify real-time changes in tumor size and location due to the current treatment. This allows the position of the patient and the planned radiation dose to be safely adjusted during treatment. This results in increased accuracy in the treatment. It can also potentially result in decreased dose and planned volume of tissue to be irradiated – if the tumor has shrunk more than initially expected, they can cut down on the dose. This allows for an overall less harmful treatment[2].

2.15 Tomotherapy

Tomotherapy is one type of image-guided intensity modulated radiation therapy characterized by the use of a helical fan beam that delivers 360 degree radiation. This machine is a cross between a CT imaging scanner and an external beam radiation therapy machine. The machine collects CT images of the tumor right before each treatment session so that immediate adjustments can be made in response to patient weight fluctuations, tumor size changes, or other noticeable differences[2].

2.16 Volumetric Modulated Arc Therapy (VMAT)

In VMAT treatments, photon beams are delivered through a single modulated arc. This maintains accuracy while dramatically speeding up treatment time. Here, an algorithm for treatment plan optimization is employed where dose is delivered during a single gantry arc with

the potential to cover 360 degrees. This technique adopts some of the techniques from tomotherapy, such as the 360 degree rotation, but differentiates itself by delivering the entire dose volume in a single machine rotation of the source[9]. One other significant advantage over tomotherapy is that VMAT can do everything that tomotherapy can do, but can also be administered through normal LINACs configured to have VMAT capability. This is very cost effective and makes this treatment incredibly feasible[10].

The use of VMAT has been steadily increasing since its onset. It was designed to make improvements from IMRT and IGRT in conformity of dose distributions, target volume coverage, sparing of normal tissues, and reduced treatment delivery time[10]. In recent years there has been an ongoing effort in the field to perform comparative studies between VMAT and the methods it was supposed to improve upon. This paper will compile some of these findings and analyze the body of results to determine whether VMAT is as effective as originally expected.

2.17 Stereotactic Radiosurgery (SRS)

SRS is characterized by its extremely accurate image-guided dose delivery. Because of this, it is able to give relatively high doses to a small tumor. The benefit of this method is high dose delivery without increased damage to normal tissues. This method, however, is limited to small tumors with clear edges and regular shapes. It is usually employed for brain or spinal tumors. In this form of photon treatment extreme head or other body part stabilization is crucial to a safely administered treatment[8]. Because of the high dose, the physicists and oncologists must be certain that they are hitting the tumor and thus the tumor region must be clearly defined.

2.18 Stereotactic Body Radiation Therapy (SBRT)

SBRT is the adaptation of SRS that treats tumors outside of the brain and spinal cord. This photon treatment type is characterized by fewer treatment sessions, smaller radiation fields, and higher doses than 3D-CRT and other conventional techniques. This technique is more susceptible to body movements and cannot be directed as precisely as SRS tumors and is therefore limited to small, isolated tumors[8]. Both SBRT and SRS use fiducial markers either on or within the patient to ensure that the dose is going to the exact location of the tumor because precision is so important in these methods[14].

2.2 Proton Therapy

While photon therapy has greatly improved since its onset with the development of more effective and safe techniques, photon therapy is still marred by the way that it deposits its energy in tissues with great entrance and exit doses. We are left wanting a better radiation therapy solution that does not litter healthy tissue with radiation on the way to the tumor. The fundamental advantage to using protons instead of photons for radiation therapy lies in the way that they deposit energy in living tissues. While photons deposit energy in small packets all

throughout their path to their intended target location, protons, on the other hand, deposit the majority of their energy at the end of their path. This allows proton therapy to reduce the radiation dose delivered to normal tissue in treatment and makes it possible to deliver higher doses to the target tumor. In addition to depositing energy in a more ideal location, protons are also higher energy than the options in photon therapy so they are more effective as well.

In addition to releasing their energy at a certain depth without significant release during travel, protons are also useful because the depth at which they release their energy can be precisely controlled[11]. The proton also releases very little energy beyond this desired depth. This allows protons to be used to treat tumors that are located against vital organs or the spinal cord, for example. To show this visually, we turn back to the Bragg peak in figure 2. Image 2B visually summarizes the clear benefits of proton therapy. These trace the path of the proton with respect to energy released and highlight the burst of energy released when they reach the site of the tumor. In proton therapy, the Bragg peak is an important tool and results in proton dose delivery that can be placed at any depth in the tissue. The radiation therapy physicists manipulate this depth by controlling the velocity of the proton[13]. What is important to reiterate in figure 2 is the differences in shape of the peaks between protons and photons. The proton peak is characterized by a low dose of radiation until the energy burst at the top of the peak and then an extremely sharp drop-off after the expulsion of radiation. This is a clear visual representation of the concept that there is limited radiation exposure to tissue as the proton travels through the body, a large dose of radiation delivered at the peak where the tumor is located, and then a sharp drop-off after dose delivery so that radiation is not delivered to healthy tissue beyond the tumor. In conclusion, the main goal in radiation therapy is to eliminate the tumor while also minimizing the damage to healthy tissue. Protons behave in such a way that the achievement of this goal is maximized. This discussion will provide a more detailed explanation of the physics that lead to the characteristics of this peak.

There are three primary types of interactions of protons in matter. These include Coulombic interactions with atomic electrons, Coulombic interactions with the atomic nucleus, and nuclear reactions. Along the course of travel, protons continuously lose kinetic energy through Coulombic interactions with atomic electrons. The rest mass of a proton, however, is 1,832 times greater than that of an electron, so therefore most protons typically travel in a straight line (figure 4A). This is therapeutically advantageous because it allows for more control over the path of the proton. In some trajectories, a proton passes close to the atomic nucleus and experiences a repulsive elastic Coulombic interaction. Because the nucleus has a large mass, this deflects the proton off of its straight line course of travel (figure 4B). Finally, it is also possible to have non-elastic nuclear reactions between traveling protons and the atomic nucleus. These interactions are far less frequent but can have much more profound effects. Here, the proton enters the nucleus and in response the nucleus may emit a proton, deuteron, triton, or neutron (figure 4C). Neutron emission is particularly dangerous during treatment and requires close attention during our comparative analysis[12]. In terms of therapeutic consideration, each of these interactions determines one dimensional component of the

treatment beam. The first interaction, inelastic Coulomb scattering pictured in figure 4A, leads to continuous energy loss that determines the depth range of beam travel in the patient. The second interaction, elastic Coulomb scattering in figure 4B, results in a change in trajectory and therefore determines the lateral penumbral sharpness of the beam. The third interaction, non-elastic nuclear reactions results in the removal of primary protons from the beam and therefore affects the fluence of the beam[12].

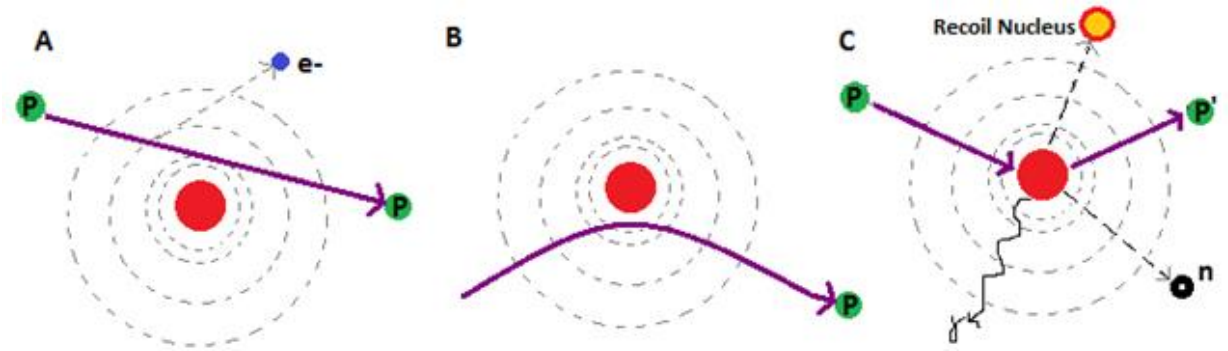

Figure 4: Schematic illustration of the three proton interaction mechanisms. Image A depicts energy loss due to inelastic Coulombic interactions. Image B depicts the deflection of proton trajectory by repulsive Coulomb elastic scattering with the nucleus. Image C depicts the removal of the primary proton and creation of secondary particles through non-elastic nuclear interactions. Here, P is a proton, e- is an electron, n is a neutron, and γ is a gamma ray.

As previously mentioned, the control of protons in proton therapy relies on the energy loss rate of ions, called linear stopping power. This is defined as the quotient of d*E* and d*x* where E is the mean energy loss and x is the distance. However, it is believed to be more convenient to express the energy loss rate such that it is independent of the mass density. The mass stopping power is defined for a beam (not a particle) as

(7) $$\frac{S}{\rho} = -\frac{dE}{\rho dx}$$

where ρ is the mass density of the absorbing material. The energy loss rate can also be described based off of the Bragg-Kleeman rule where the energy loss rate is

(8) $$\frac{S}{\rho} = -\frac{dE}{\rho dx} \approx -\frac{E^{1-p}}{\rho \alpha p}$$

where ρ is the mass density of the material, α is a material-dependent constant, E is the energy of the proton beam, and p is a constant that is included to take into account the proton beam energy's dependence on velocity[12]. Because the first form of interactions of protons in matter (figure 4A) is most common, it is most physically meaningful to state that the linear stopping power is proportional to the density of electrons in the absorber. Essentially, components such as the velocity of the proton and the absorber material can strongly influence the energy loss

rate. The material density in the human body can vary by about three orders of magnitude from air in the lung to cortical bone[12]. Therefore, when a treatment is plan is created, the specific path in the body that the proton will take is a critical piece of the plan.

Another important consideration when seeking to understand the behavior of protons in radiation therapy is range. In this case, range is defined as the depth in which half of the protons in the medium have come to rest[12]. There are small fluctuations in the energy loss of individual protons, which is called range straggling, so as a result range is an average quantity. The range is therefore defined for a beam and not for individual particles. Overall, however, the proton path length is effectively a straight line with a path length nearly equal to its projected range. Range may be calculated by

(9)
$$R(E) = \int_0^E \left(\frac{\mathrm{d}E'}{\mathrm{d}x}\right)^{-1} \mathrm{d}E' \approx \sum_0^E \left(\frac{\mathrm{d}E'}{\mathrm{d}x}\right)^{-1} \mathrm{d}E',$$

where E is the ion's initial kinetic energy and the summation represents the calculation of continuous transport approximated by calculations in discrete steps[12].

The range can also be calculated by using an analytical approach. This depends on the knowledge that the proton range of interest can be as deep as 30 cm (the midline of a large male's pelvis which is considered to be the deepest point in the human body) and as near as 1mm. This range corresponds to 11 MeV and 220 MeV[12]. The correlation between the logarithm of range and logarithm of energy has been found to be linear which means that the range of the proton may be calculated following a simple power law. This is the Bragg-Kleemann rule for range where

(10)
$$R(E) = \alpha E^p$$

and again α is the material dependent constant, E is the initial energy of the proton beam, and p accounts for the dependence of the proton's energy or velocity.

The next important consideration is lateral scattering from elastic Coulomb scattering due to interactions with the nucleus. Even a small change in proton trajectory is important and must be taken into account when designing beamlines and calculating dose distributions in patients. To characterize the amount that the beam is misshaped by scattering, physicists calculate the quantity of scattering power

(11)
$$T = \mathrm{d}\left\langle\theta^2\right\rangle / \mathrm{d}x,$$

where $\langle\Theta^2\rangle$ is the mean squared scattering angle and x is the thickness of the absorber (so for therapeutic purposes, human tissue). In addition to this, the mass scattering power is T/ρ where ρ is the mass density of the absorber material. When developing predictions of elastic Coulomb scattering, the number of scattering events N_s that occur in a given absorber is used. For multiple Coulomb scattering, the combined effect of all N_s events can be statistically modeled. This statistical approach can predict the probability for a proton to scatter by a net angle of deflection. The most complete theory for clinical proton therapy is the Moliere theory which focuses on the net effect that many small angle scattering events have on the collection of protons. This translates to an understanding of lateral spatial distribution of dose in a patient. Using the small angle approximation, Moliere theory is described by

(12) $$P(\theta) = \eta d\eta \left(2\exp\left(-\eta^2\right) + \frac{F_1(\eta)}{B} + \frac{F_2(\eta)}{B^2}\cdots\right)$$

where $\eta=\Theta/(\Theta_1 B^{1/2})$, $\Theta_1=0.3965(zZ/\rho\beta)\text{root}(\rho\delta x/A)$ and d(Ω) is the solid angle that the particles are scattered through. Z is the atomic number, A is the atomic mass, δx is the thickness, ρ is the mass density, z is the proton charge, $\beta=v/c$, and B can be found by solving $g(B)=\ln B-B+\ln\Upsilon-0.154=0$. In this equation for B, $\Upsilon=8831qz^2\,\rho\delta x/(\beta^2 A\Delta)$, and $\Delta=1.13+3.76(Zz/137\beta)^2$. Finally, the $F_k(\eta)$ functions are defined as

(13) $$F_k(\eta) = \frac{1}{k!}\int J_0(\eta y)\exp\left(\frac{-y^2}{4}\right)\left[\frac{y^2}{4}\ln\left(\frac{y^2}{4}\right)\right]^k y\,dy,$$

and $J_o(\eta\Upsilon)$ is a Bessel function. This is a very complicated theory and simpler versions and alternatives do exist. However, the simpler alternatives are not nearly as accurate and the Moliere theory is the most respected and relied on[13].

In some aspects of proton theory, this multiple Coulomb scattering is useful because it allows intentional beam spread and thickening so that the tumor can be completely covered with a uniform dose. However, uncontrolled multiple Coulomb scattering in the treatment head and within the patient blurs the lateral sharpness of the treatment[13]. In order to use proton therapy to its maximum potential and harness the method into a truly effective tool, we must understand how to preserve this lateral penumbral sharpness to a very precise degree.

The final “dimension” affecting control of proton therapy that must be considered is beam fluence changes due to nuclear interactions. This results in a decrease in absorbed dose due to the removal of primary protons. This is partially replenished by secondary protons that result from these interactions and deliver dose. However, the other side of the emission of secondary protons is minor decreases in beam conformity. Another more hazardous result of non-elastic nuclear interactions is the production of free neutrons. These are extremely penetrating and have relative biologic effectiveness up to 20 times higher than that of proton radiation[13]. These free neutrons can lead to a variety of health issues which will be discussed

further. Efforts to minimize this byproduct of proton therapy have been employed and are crucial to the safe delivery of proton therapy.

2.3 Electron Therapy

Electron therapy is the second main form of charged particle radiation therapy. Because of their lower energy level, electron beams cannot travel far through the body. The most clinically useful energy range for electrons is 6 to 20 MeV[15]. Electron therapy treatment, however, is very effective. For this reason it is widely used to treat superficial tumors such as skin cancers on or near the surface of the body[11]. At this energy range, electron beams can treat tumors less than 5 cm deep[15]. While this limits the variety of uses for electron radiation, it is also an advantage because the electrons are able to treat superficial cancers without penetrating too deep into the body and harming healthy tissues[11]. The electron therapy beam is characterized by a sharp drop-off (similar to that of proton beams) in dose beyond the tumor[15]. While this is part of its range limitation, it also allows for safe delivery because the dose is highly controlled with depth and it spares healthy tissues. Overall, there are five main categories of therapies that are good fits with electron therapy: treatment of skin and lip cancers, chest wall irradiation for breast cancer, administering boost dose to nodes, and treatment of head and neck cancers[15]. The processes of energy loss, interactions with atoms, and dose delivery are very similar between electrons and protons. Electrons interact with atoms in the absorber in the same way that protons do and the stopping power is determined by the sum of collisional losses and radiation losses. One difference is that electrons are far more susceptible to scattering with a scatter pattern that can be modeled by a Gaussian distribution. This leads to issues with dose delivery sharpness and must be taken into account. Overall, the main difference between electron and proton radiation is the scale, with electrons being much smaller than protons and the same size as the electrons that they interact with, but this simply results in the limited depth that differentiates electron therapy from proton therapy.

3. Comparative Review of the Most Commonly Used and Most Effective Treatment Methods

For the comparison in the current paper, the focus is on the particle and photon treatment modes that are most often used or most highly researched and show significant therapeutic potential. This includes intensity modulated radiation therapy, 3D conventional radiation therapy, volumetric modulated arc therapy, image guided radiation therapy, 2D conventional radiation therapy, and various types or proton therapy, among other forms. We analyzed the body of research discussing each type of radiation therapy technique and its strengths and weakness and developed what we believe to be the five categories of consideration that are of the greatest importance when conducting a comparative analysis of these treatment modalities and planning a cancer treatment. These include precision and specificity of delivery, dose delivered to healthy tissue and associated risks, risk of second cancer, time that the treatment takes, and feasibility of treatment.

3.1 Precision and Specificity of Delivery

When discussing the effectiveness of each form of radiation therapy, the first step is a brief analysis of relative abilities to achieve maximum dose delivery precision for each method of radiation delivery and each form of radiation. From here we can dive deeper and tackle other implications of dose control and analyze the overall performance of each method of delivery. Several innovations have led to drastically improved precision in beam conformation and delivery. The most notable are the advancements in imaging and the onset of image guided therapy, the use of intensity modulated therapies that control the exact dose delivered to each region of the target area, and the development of tools that can account for limited specificity within certain delivery methods. When we discuss precision in radiotherapy we are referring to the precise delivery of radiation to targeted areas by combined utilization of radiotherapy, computing, and physics[16]. This is characterized by four qualities: the delivery of very high radiation doses to targeted tumors, limited exposure of normal tissue to radiation, precise dose homogeneity and conformity and attention to treatment plan quality, and precise localization of the tumor area. In our comparative research through the literature, we found that proton radiation therapy was on the high end of the precision scale and that several photon therapy methods including IMRT, SRS, IGRT, and VMAT rivaled this precision.

Proton therapy is inherently precise because of the large size of protons and their ability to penetrate human tissue, whereas electron therapy is characterized by scattering and concerns about particle control. Once minor beam variation due to the small angle redirection of protons through repulsive Coulomb elastic scattering is accounted for, proton beams are able to precisely deliver their dose to the desired range. Even with this slight lateral scattering, the lateral scatter in proton therapy is significantly less than the amount of lateral scatter in photon therapy[25]. Many studies have verified that proton therapy delivers a more uniform and precise dose than respective photon therapies. We specifically studied several papers that reported significant improvements in control of craniospinal irradiation with proton therapy. These included the studies by Lee et al., Miralbell et al., Slater et al., and St Clair et al. While each of these studies had relatively small sample sizes, the results were consistent across each study and supported the precision of proton therapy over photon therapy[18,19,20,21]. The more recent paper by Howell et al. conducted a similar study to these and compared therapeutic dose distributions for photon and proton craniospinal irradiation for a group of 18 patients. The patients underwent CT simulation and then treatment plans for proton and conventional photon therapy were created and analyzed. They found that proton craniospinal irradiation provided more homogeneous target coverage and conformation to the target region than photon therapy for patients across a wide age and BMI spectrum[22]. This indicates an overall greater level of treatment control and precision in proton therapy.

The only major concern within proton therapy is the production of secondary particles such as free neutrons. The path of these particles is not directed or controlled and they can lead to health concerns. There are three distinct sources of radiation exposure during

treatment, all illustrated in figure 5. The beneficial and purposeful radiation is the therapeutic protons pictured in red. The second is stray neutrons from the treatment apparatus pictured in blue. The third, also pictured in blue and marked by horizontal arrows, is neutrons produced by therapeutic proton radiation inside of the body. When the proton beam is created, a small-diameter beam of protons enters the treatment apparatus. The apparatus spreads the beam to a clinically useful size and collimates it to the desired target size that will irradiate the tumor and spare healthy tissue. Within the treatment apparatus, proton induced nuclear reactions can take place, which yields stray neutrons which can leak out and irradiate the patient. Again, these reactions can also take place within the patient. These neutrons provide no therapeutic benefit and increase the risk of radiogenic side effects[12].

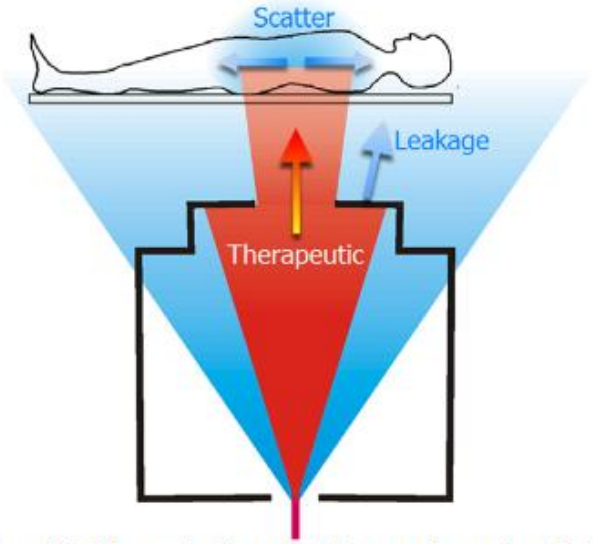

Figure 5: Schematic diagram of proton beam irradiation of the spine. The red area represents therapeutic proton dose, the blue area represents stray neutrons leaking out of the treatment aparatus, and neutrons produced by therapeutic proton radiation inside the body (also blue marked by horizontal arrows). These are the three distinct sources of radiation exposure. Image adapted from Newhauser et al. 2015.

Some have said that while proton therapy is incredibly promising, its use is not justified because of incomplete research on the dangers of stray neutron exposure[27]. This is a partial hole in understanding in the field that more research should be dedicated to. Proton therapy is one of the hardest therapy forms to simulate, so these studies are a bit more difficult than similar studies in photon therapy. While this is an important area to dedicate more research, some promising studies have been published recently. In one study, it was found that the risk or radiogenic side effects from stray radiation is small but not negligible. However, the risk posed from using photon therapy rather than proton therapy is even greater[12]. Taddei et al. found that by adding shields near the patient, using a tungsten-alloy collimator, and adding an

upstream collimator after the range shifter assembly, they were able to reduce the neutron dose by 66% in prostate cancer patients[28]. Currently, there are several good Monte Carlo simulations that model stray neutron dose. Future research in this area should focus their efforts on developing stray dose algorithms that are possible to implement into treatment planning programs and used for clinical purposes. Brenner et al. did some preliminary research on ways to limit stray neutron dose and found that various pre-collimator and collimator combinations with different geometries, distances, and materials paired with various proton energies greatly affected the stray dose. These factors could be combined to form an optimized design for each treatment case to significantly reduce stray neutron dose[29]. This optimization may be a good starting point for algorithm development and future research.

For photon therapy, IMRT is at the top of the discussion about precision because not only does it utilize extremely specific multi-leaf collimators that allow for precision in the shape of the beam relative to the tumor, but it also delivers a different dose to each region of the tumor and controls the dose to deliver a low but deliberate dose to healthy tissue neighboring the cancer region. Within each beam there are beamlets of different intensity levels that allow for a huge degree of freedom to create a precise treatment plan. Various studies such as Teoh et al.[10] and Chang et al.[24] have experimentally determined that IMRT has significantly greater dose control than other more primitive photon therapies. Chang et al. studied 25 patients with medically inoperable Stage I or Stage III non-small-cell lung cancer (NSCLC). They compared the 3D-CRT, IMRT, and proton radiotherapy. They found that proton radiotherapy had the overall best performance and delivered the most controlled dose, but that IMRT was able to achieve a much greater dose escalation than 3D-CRT without losing control of radiation placement[24].

The paper by Teoh et al. discussed advantages in VMAT precision in terms of its ability to allow for the simultaneous variation of three parameters during treatment. These included gantry rotation speed, treatment aperture shape with the use of multi-leaf collimators, and dose rate. Where IMRT requires the use of many superimposed arcs to achieve their dose distribution, VMAT can treat the entire target volume using one or two arcs. Essentially, it is a form of single arc intensity modulated therapy that can also use dose rate variation[10]. In the study by Cozzi et al., they conducted a planning study comparing VMAT with IMRT in eight patients with cervical cancer. The results showed similar target volume coverage between the two, but VMAT demonstrated improved dose homogeneity and conformity[17].

The studies discussed above indicate that VMAT can do more and has the ability to improve its precision rating based on a greater number of variables that can be adjusted to perfectly fulfill a treatment plan. However, when we compare quality assurance between VMAT and IMRT, looking at the raw ability of the two methods to accurately carry out a treatment plan without too much rogue dose delivery and variation, they preformed similarly. The study by Mancuso et al. constructed treatment plans for both VMAT and IMRT. The plans were repeatedly delivered across multiple measurement sessions and the resulting dose distributions were measured using both radiochromic film and ionization chamber and a commercial two-

dimensional diode array. The QA measurements from each delivery technique were analyzed, compared, and run through a statistical analysis. They found that of the 22 comparisons IMRT showed better QA results in 11 cases and VMAT showed better QA results in 11 cases. So, although differences between the two plans were noted, neither mode of dose delivery showed consistently better precision[26].

Image guided radiation therapy benefits from the implementation of imaging throughout the treatment session so that the precision of photon therapy can be maximized through a greater understanding of the location and shape of the tumor throughout treatment. IGRT is most often used in conjunction with IMRT to create a very precise proton therapy treatment plan[2]. However, a major hole in the body of radiation therapy research is the need to develop an understanding of the best way to guide radiotherapy with the images produced, either for target volume definition or prognosis stratification[16]. Future studies on IGRT should seek to translate precise target delineation into better tumor control and integrate it more deeply into the treatment process so that the two processes (imaging and treatment) are not two separate steps but rather one imaging process that dictates the implementation of the other.

In certain cases, it is not feasible to use the most precise methods of radiation therapy delivery. In these cases, adjustments must be made to provide safe and controlled therapy with conventional treatment methods. For example, as discussed above, 2D-CRT has many significant disadvantages (such as skin burns, lack of dose control, and the development of hot spots in the patient), but is still used when immediate radiation therapy is required because of the method's allowance for the rapid development of treatment plans and fast administration. An important development is the use of individually shaped bolus to minimize dosimetric heterogeneities. This means that they are reducing hot spots in thinner regions of anatomy and cold spots in thicker regions[22]. This forces dose conformity and homogeneity. Bolus is a material which has properties equivalent to tissue when irradiated. When placed on the surface of a human receiving therapy, bolus can be used to alter dosing. It is most often used in cases of irregular tissue shape which result from normal (or abnormal) variations in the shape of the human body. Bolus can be polythene bags that take the shape of the skin surface, certain waxes sculpted to fit the specific shape needed by the radiation physicist, or Perspex which is acrylic glass. It can both serve as a missing tissue compensator to level the tissue or as a way to increase the dose to the patient's external surface (mostly for electron therapy)[23]. Several groups are doing research on bolus therapy and improving bolus effectiveness. This is an important direction in the field so that precision can be maximized no matter which method of delivery is available.

3.2 Dose Delivered to Healthy Tissues

Directly related to precision of delivery method is the dose delivered to healthy tissues. This is the next step in the analysis after beam control and precision and includes a variety of negative side effects. When broadly comparing proton therapy to photon therapy with dose

delivered to healthy tissue in mind, we must return to figure 2 with the Bragg peak representing the dose delivery pattern of these two forms of radiation therapy. Again, a very clear model of the increased dose delivered to healthy tissue in photon therapy is the entrance dose and exit dose regions in the Bragg curve. Proton therapy is inherently structured so that the dose is not delivered until the proton beam reaches its desired depth. Photon radiation is expelled with enough energy to deliver a significant dose to the desired depth, but results in significant irradiation of the tissues on the way into the body and past the tumor. With photon therapy the idea of depth is less concrete and does not represent the area of dose delivery but rather a stop along the path of exponentially decreasing tissue irradiation from the skin to the point when the beam runs out of energy. This is the underlying feature driving the following comparisons investigating the dose of radiation delivered to normal tissues.

Zhang and colleagues compared proton and photon therapies in terms of predicted risk of second cancer for a 4 year old medulloblastoma patient receiving craniospinal radiation. They compared a passive scatter proton therapy beam line with intensity modulated photon therapy. Their results show an example of the realization of the implications in the Bragg curve of figure 2. Figure 6 shows the absorbed dose distributions for this 4 year old boy's treatment. Figure 6A shows the photon therapeutic absorbed dose distribution and 6B shows the proton therapeutic absorbed dose distribution. In the photon dose image, the dose fall off is much more gradual than that of the proton image. This is highlighting the effect magnitude of the exit dose marked in figure 2. The proton dose stays in the craniospinal region, but the photon plan spreads radiation to all of the critically important organs in the surrounding area. Finally, image 6C is the stray neutron dose distribution from proton therapy. While the dose is far lower in magnitude than the therapeutic proton dose, this image does a good job of highlighting how widely stray neutrons are able to penetrate the body and invade healthy tissues[31].

This paper is limited by the single-patient sample size. The nature of the comparison, between two verified best-option treatment plans, allowed for this sample size to be relatively reasonable. However, it would be important to make similar comparisons in future studies using larger sample sizes with a variety of ages and genders.

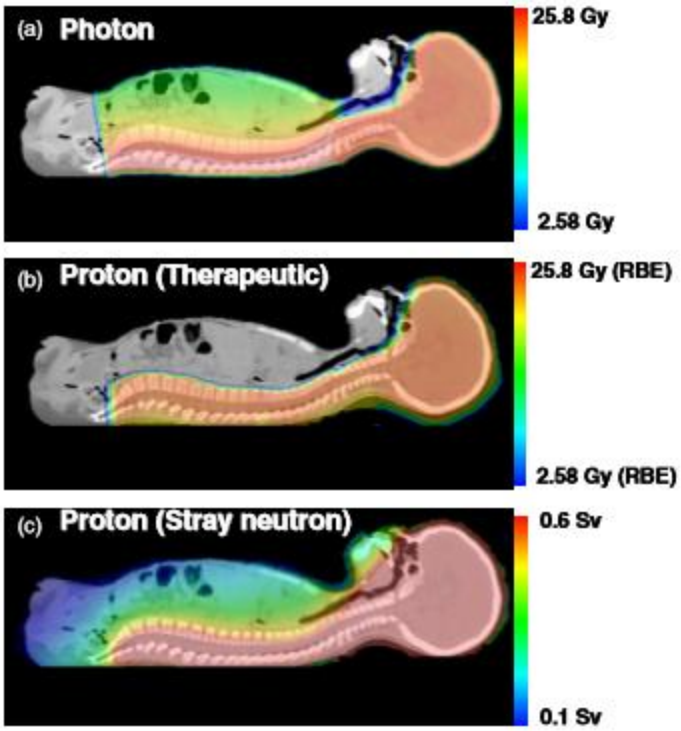

Figure 6: Dose distributions for a 4 year old boy receiving craniospinal irradiation. Image A shows the dose distribution for photon irradiation, image B shows the dose distribution for therapeutic proton irradiation, and image C shows the dose distribution for stray neutrons that result from proton therapy. Image adapted from Zhang et al. 2013.

The study by Howell et al. is similar to the work by Zhang and colleagues, but compared conventional photon therapy to proton therapy for craniospinal irradiations (CSI) for medulloblastoma. They developed photon and proton treatment plans for 18 patients, including both males and females with various ages and builds. They found that proton CSI spared normal tissues significantly better than photon CSI. Figure 7 shows the dose distributions for photon and proton treatment plans for a representative patient. In these images the 100% dose line (red) indicates the intended treatment region. From the figures we can see that the prescribed dose covers all of the vertebral bodies in the proton plan but only covers the spinal canal in the photon plan. We can also see that the proton dose quickly decreases after the 100% dose line and the photon plan delivers significant dose far outside of this region. As a result of this, we also notice that tissues and organs near the target volume are exposed to significantly lower doses in the proton plan than in the photon plan. This is also represented in the dose volume histogram of figure 8 where we can clearly compare the dose that each important organ receives between photon treatment and proton treatment. In essentially every organ the radiation exposure differences are very clearly significant to the

naked eye. Across the board photon therapy exposes healthy organs to a greater dose (figure 8). Quantitatively, they found that on average the photon plans were 8% hotter than the proton plans. The dose to healthy organs was especially bad in the organs that were located anterior to the target region because of the strong entrance dose[22].

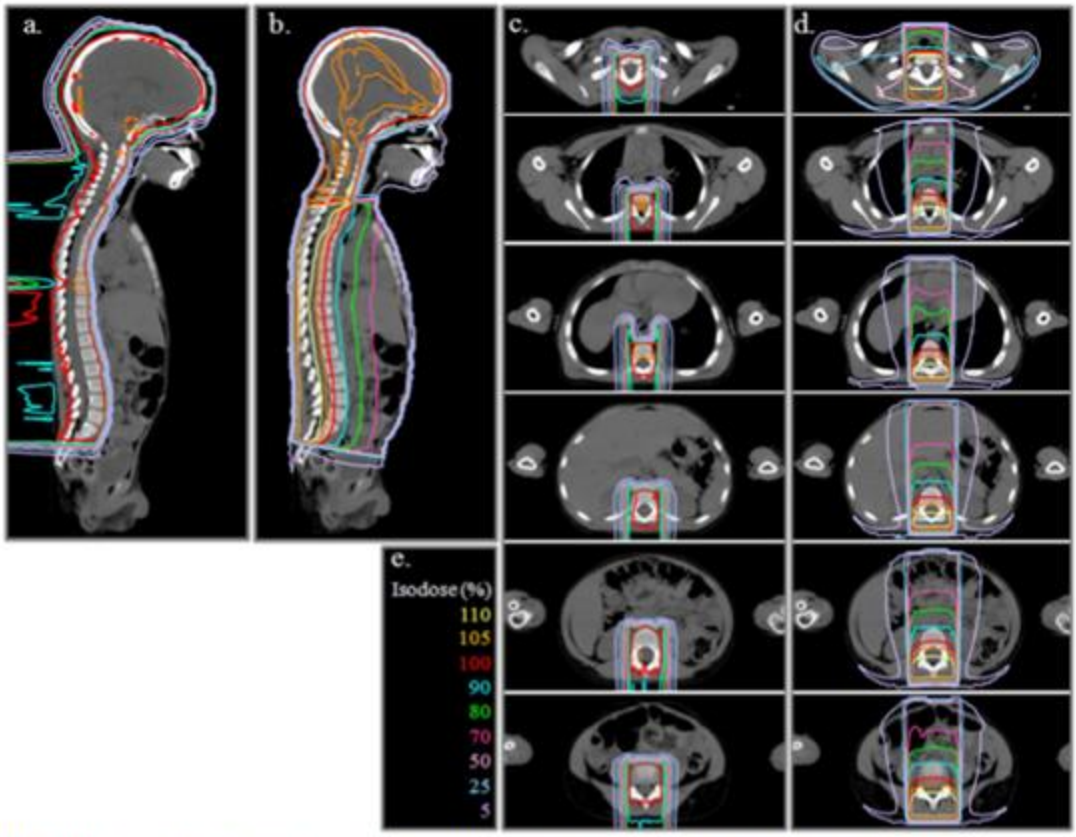

Figure 7: Photon and proton treatment plans for a representetive patient receiving CSI for medulloblastoma. Image a is the proton dose distribution in the sagittal plane. Image b is the photon dose distribution in the sagital plane. C is the proton dose distribution in axial planes from the cervical spine to the sacral spine in 5cm increments. D is the photon dose distribution for the same axial planes. E is the isodose scale for both treatment plans. Throughout the images, the red line is the 100% isodose line that indicates the intended treatment region. Image adapted from Howell et al. 2012.

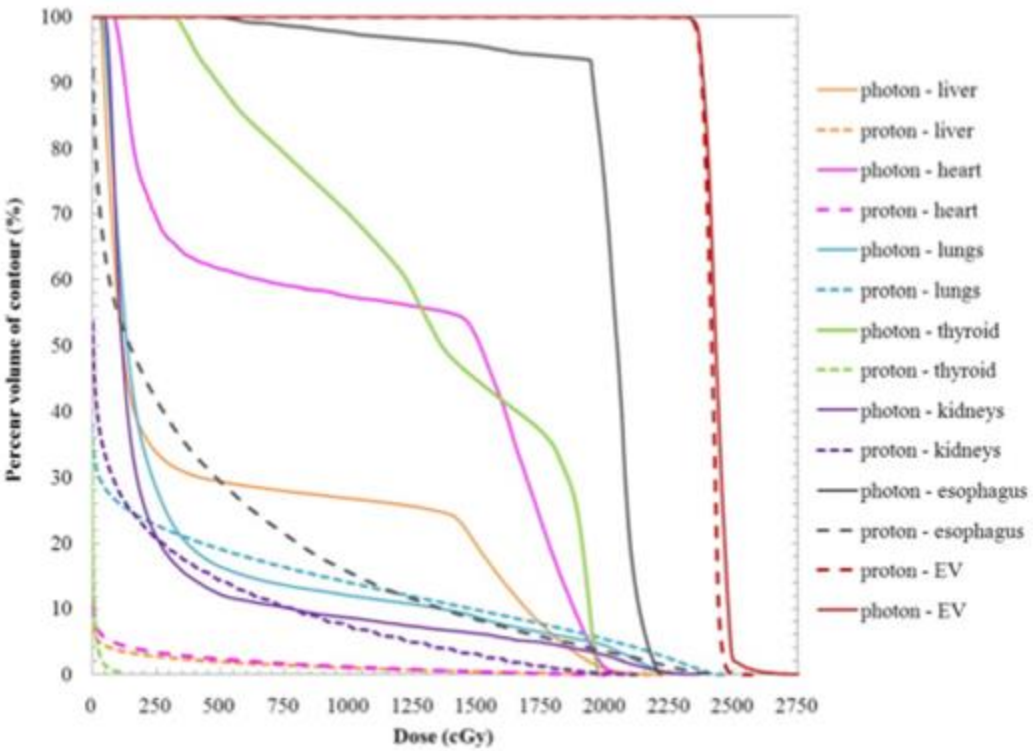

Figure 8: Photon and proton dose volume histogram (DVH) for a representative patient. The dotted lines represent proton DVHs and the solid lines represent photon DVHs. The absolute dose values are on the horizontal axis and the percent volume of contour is on the vertical axis. Image adapted from Howell et al. 2012.

Another study, by Chang and colleagues, tackled the comparison of dose to normal tissue between 3D-CRT, IMRT, and proton therapy for 25 patients with Stage I or Stage III lung cancer. First, they found that proton radiotherapy reduced the normal tissue dose in Stage I and Stage III lung cancer compared with 3D-CRT. In this treatment comparison they found that proton therapy spared the contralateral lung, heart, spinal cord, and esophagus. It also reduced the low-dose exposure in the ipsilateral lung. The mean total lung dose was 9.7 Gy for photon therapy with a prescribed dose of 66 Gy whereas the dose was 5.4 Gy for proton therapy with a prescribed dose of 66 CGE. This resulted in an absolute improvement of 19%. The total body mean non-target dose was reduced from 5.3 Gy at 66 Gy photon therapy to 2.1 Gy at 66 CGE proton therapy which is a 61% absolute improvement. The rest of the organ results can be visualized in the dose value histogram in figure 9. It is clear to the naked eye that proton therapy greatly improves upon photon therapy. The results were similar for comparisons between proton radiotherapy and 3D-CRT in Stage III lung cancer.

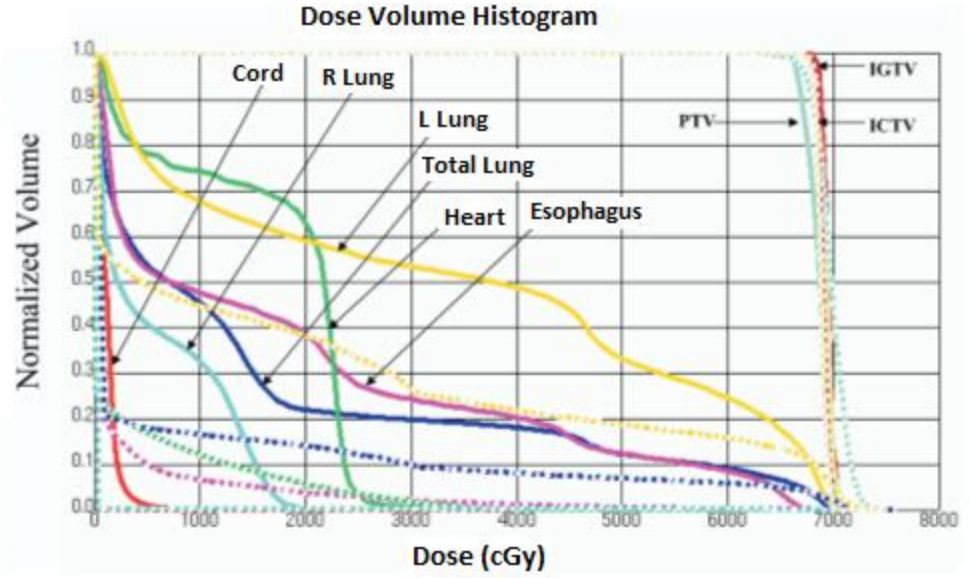

Figure 9: Dose volume histogtam for photon 3D-CRT (solid line) and proton radiotherapy (dotted line) for a patient with non-small-cell lung cancer treated with 66 Gy. Each pair of colored lines (labeled) represents a different organ or sensitive area. Image adapted from Chang et al.

For the comparison between IMRT and proton therapy, they found that proton therapy reduced the dose to normal tissue compared with IMRT. Here doses to the lung, heart, spinal cord, and esophagus were again reduced. For the patients treated with IMRT, the mean lung dose was 20.1 Gy for photon therapy at the prescribed 60 Gy dose and 17.5 Gy for proton therapy at that dose. The body mean non-target dose was 6.8 Gy at a prescribed 63 Gy dose for photon therapy and 4.5 Gy at 63 Gy with proton therapy. This was a 34% improvement. We see here that even with the improvements that IMRT makes upon 3D-CRT, the advantage is still clearly in favor of proton therapy. This is pictured, for the rest of the organs as well, in the DVH in figure 10. Again, the difference is quite clear visually.

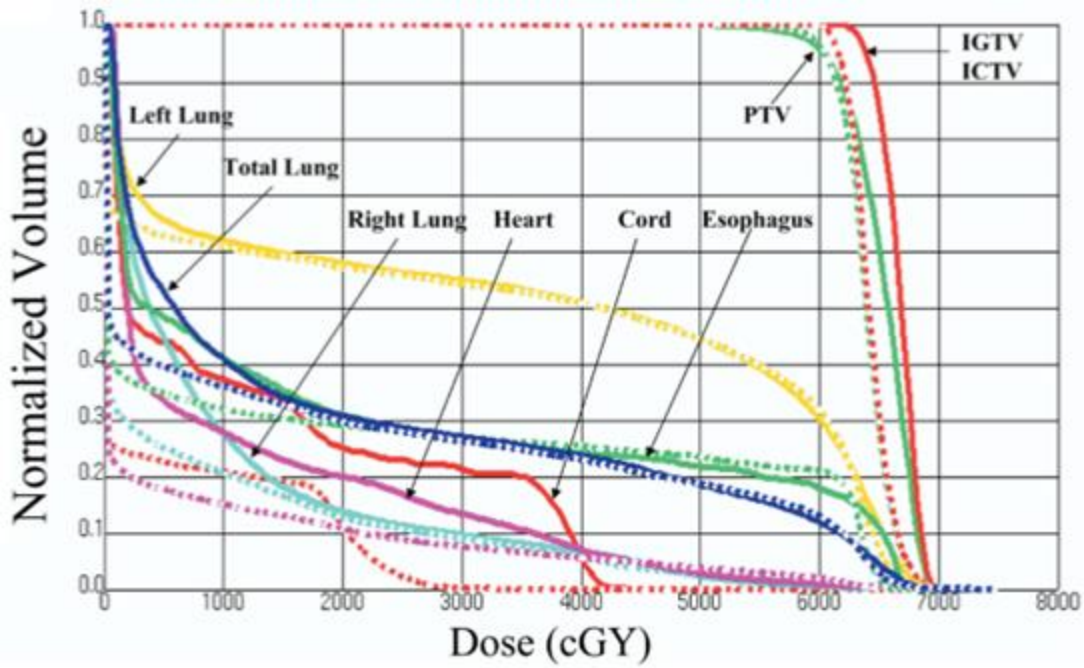

Figure10: Dose value histogram for the comparison between IMRT and proton therapy for various organs near the lung target region in a patient with Stage III non-small-cell lung cancer. The solid line is the IMRT photon therapy dose and the dotted line is the proton therapy dose. Image adapted from Chang et al.

Overall they found that in each case, proton treatment significantly reduced the dose to the lungs, esophagus, spinal cord, and heart. Additionally, the non-target integral dose had a 33-61% absolute improvement with proton therapy. Notably, in stage I disease, proton therapy treatment almost completely spared the contralateral lung, heart, esophagus, and spinal cord. Finally, it is important to consider that with lung cancer treatment, respiratory motion adds a great level of complexity and danger to treatment. We recall that IMRT is able to reduce normal tissue toxicity in many cases, but its high dose gradient and conformity require a very high level of precision in dose delivery and therefore tumor localization. Therefore, a moving tumor makes IMRT less effective. This allows the proton therapy to demonstrate even greater strength because each proton beam typically treats all target volume, not just a portion like IMRT does. This results in proton treatment being more effective for a moving target[24].

It has been demonstrated that VMAT delivers a comparable or decreased dose to healthy tissues and organs at risk than IMRT[10]. One earlier study, by Cozzi et al., found that VMAT reduced the dose to healthy tissues by 12% compared with IMRT[17]. Rotational arc therapy distributes a lower dose over a larger volume of normal tissue than static beam radiotherapy[30]. Because of these differences, it is important to study the dose distribution in arc therapy. In the recent study by Rechner and colleagues, they compared the dose distributions between VMAT and proton arc therapy. They found that the VMAT and proton arc

therapy treatment plans sufficiently covered the target, where at least 99% of the planning target volume (PTV) received at least 76 Gy of dose. Figure 11 shows that proton arc therapy delivered a lower dose over a smaller volume of normal tissue than VMAT. This is clearly illustrated in figure 11 where the dose VMAT in image 11A seems to flood the body. It is noteworthy that the high dose is certainly restricted to the PTV, but the significance lies in the comparison between the two methods where proton arc therapy is clearly more controlled and does a far greater job of keeping the dose from irradiating healthy tissues. Numerically, they found that on average, proton arc therapy reduced the volume of normal tissue receiving doses between 10 and 30 Gy by 73% compared with $VMAT_{30}$.

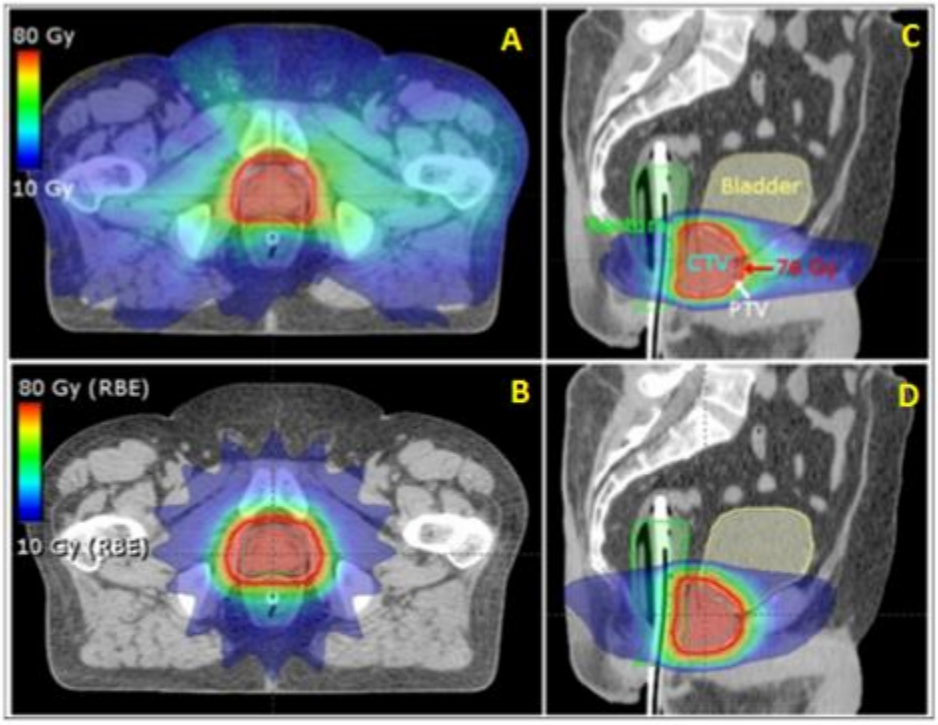

Figure11: Dose distribution plans for radiation therapy of a prostate cancer patient. The left hand column, images a and b, are axial images and the right hand column, images c and d are sagittal images. Images a and c show the dose distribution delivered through VMAT treatment and images b and d show the dose distribution delivered through proton arc therapy. Image adapted from Rechner et al. 2012.

Finally, it is important to touch upon the variety of health concerns that significant radiation dose exposure to healthy tissues can cause before diving into one of the most significant negative effects, the development of second cancers. Merchant and colleagues conducted a study in pediatric brain tumors to compare photon and proton therapy dose characteristics and their relationship to cognitive function. They used models that have been developed to correlate radiation dose to normal tissue volumes with functional outcomes. They have found links between normal tissue irradiation and abnormalities in growth and

development and endocrine and cognitive function. Using a sample size of 40 cases, they studied four types of childhood brain tumors, optic pathway glioma (OPG), craniopharyngioma (CR), infratentorial ependymoma (EP), and standard risk medulloblastoma (MB), and found that proton beam therapy was able to improve outcomes for children with brain tumors because of its ability to reduce dose to normal tissues. The dose volume histograms in figure 12 show the difference in the volume of normal tissue exposure to radiation between photon therapy (red) and proton therapy (blue) in the hypothalamus, left temporal lobe, left cochlea, and total brain.

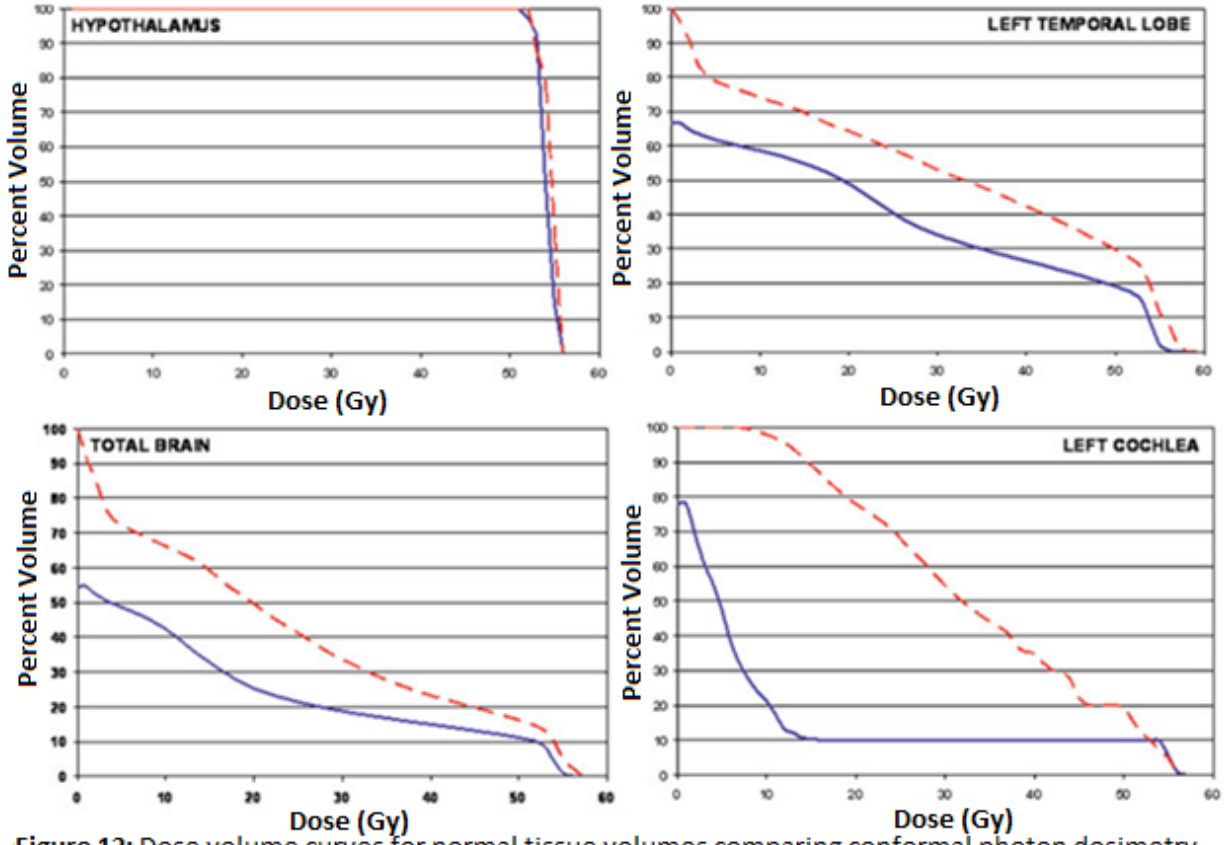

Figure 12: Dose volume curves for normal tissue volumes comparing conformal photon dosimetry (red) with proton beam dosimetry (blue). These curves are the averages from 10 cases of optic pathway glioma. The respective curves for the other brain tumor types showed similar trends. Image adapted from Merchant et al.

They then compared model-estimated spelling scores on the Wechsler Intelligence Test (WIAT) from normal tissue brain dosimetry values for both forms of radiation. This led to the determination of the estimated IQ score as a result of radiation. They found that in OPG, MB, and CR, there was a significant difference in IQ outcomes between proton and photon therapy with proton therapy preserving cognitive function more effectively. They were not able to make a comparison for patients with EP. Figure 13 shows a representative IQ plot showing the difference in estimated WIAT score for patients with OPG planned for treatment with proton therapy (blue) and photon therapy (red). As time after treatment increases, the differences in IQ become more profound.

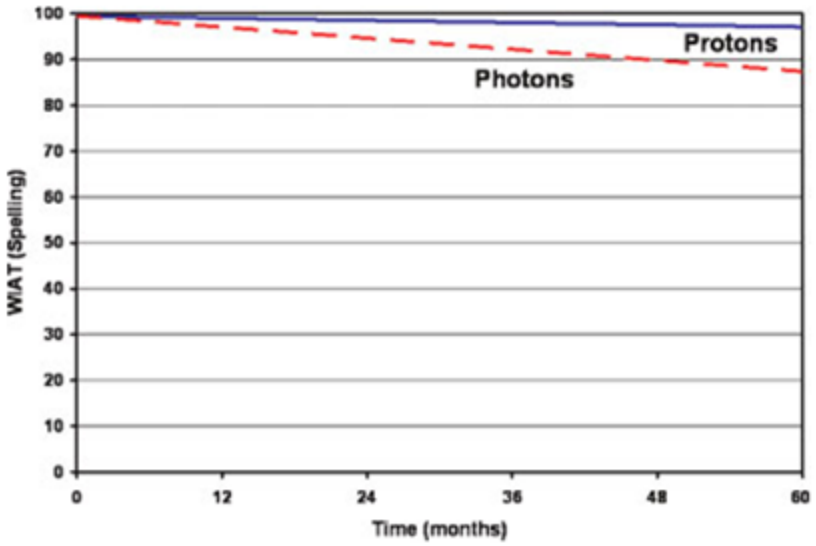

Figure13: Estimated WIAT spelling score (representing IQ) for patients with optic pathway glioma planned for treatment with scanning proton beam therapy (blue) and conformal photon radiation therapy (red).
Image adapted from Merchant et al.

They also considered the effects of radiation therapy on growth hormone deficiency. The dose to the hypothalamic-pituitary axis predicts endocrinopathy in patients. They found that in patients with EP, proton therapy can avoid growth hormone deficiency, based on location and size of the tumor. For patients with MB, the strength of the dose of radiation to the tumor determines whether or not there will be negative endocrine side effects. It is easier to spare tissues from high dose radiation with proton therapy than photon therapy and this modality was therefore found to reduce central hypothyroidism, gonadotropin insufficiency, and adrenal insufficiency. Finally, they considered hearing loss, which can be a result of brain tumor irradiation. They found that in all cases across all tumor types, the protons provided dose distributions that were significantly below the threshold for radiation induced hearing loss[25].

3.3 Risk of the Development of Second Cancers

When discussing the variety of serious side effects that can occur when normal tissue gets too great a dose during radiation therapy, one of the most serious is the development of second cancers, which falls into the category of “negative late effects” because of its late onset (on the scale of years) after cancer treatment. After smoking, the development of second cancer as a result of normal tissue exposure to radiation is the second most studied carcinogen[3]. While the individual risk of developing a second cancer after radiation therapy is often quite low, there are, for example, on the order of 3,000 new cases of cancer caused by radiotherapy in the prostate alone each year[30]. This means that any reduction in risk of the development of second cancer could have a very significant impact on public health across the

board. In this section we will also discuss studies that demonstrate how the dose delivered to healthy tissue can result in the development of second cancers.

IMRT plans use a larger number of monitor units (MU) compared with conventional plans and proton therapy. This leads to an increase in the amount of low dose radiation to healthy tissues. This increase has led to concerns of increased risk of secondary radiation-induced malignancies. VMAT achieves many of the benefits of IMRT while significantly reducing the use of MU[10]. While IMRT has many great advantages, preventing second cancer may not be one of them. In fact, one early study suggested that the incidence of second cancers may nearly double with IMRT compared with conventional radiation therapy (from 1% to 1.75% for patients surviving 10 years)[27]. Because of these initial findings in the early research, we thought a comparison between IMRT, VMAT, proton therapy, and conventional radiotherapy as it relates to secondary malignancies in recent research was critical to this discussion.

First, one study by Fontenot and colleagues assessed the risk of second cancers from proton therapy relative to IMRT. They considered both primary and secondary sources of cancer and focused their research on prostate cancer. They created treatment plans and ran their results through risk models from the Committee on the Biological Effects of Ionizing Radiation. They found that proton therapy reduced the risk of secondary cancer by 26-39% compared with IMRT. Even in organs directly in field of the treatment path, proton therapy greatly reduced the risk of second cancers compared with photon therapy.

Next, the study by Brodin and colleagues compared the risk of second cancers in pediatric patients with MB treated with 3D-CRT, inversely optimized arc therapy, or intensity modulated proton therapy. They found that estimates of second cancer risk were highest for arc therapy treatment. However, they also found that the risk of developing heart failure, hearing loss, hypothyroidism, and xerostomia was highest for 3D-CRT. The risk of all adverse effects was lowest for proton therapy plans. This is with the inclusion of secondary neutron dose. Photon therapy does not lead to secondary neutron radiation, but this study and others demonstrate that even with that photon therapy advantage, proton therapy is still far safer when it comes to adverse effects. They estimated that the risk of second cancers in this type of cancer was 45%, 56%, and 7% for 3D-CRT, arc therapy, and proton therapy for 23.4Gy prescribed dose, respectively. For 36 Gy prescribed dose, the risk of second cancer development over the patient lifetime was 54%, 71%, and 9% for 3D-CRT, arc therapy, and proton therapy, respectively. In figure 14A we see the dose distributions from the three treatment types noting that, again, proton therapy has the smallest dose range with limited dose spreading to healthy tissues. Figure 14B shows a plot of the absolute risk of the development of second cancers after each of these treatments. The volume of normal tissue irradiated appears to directly correlate to risk of second cancer yet again.

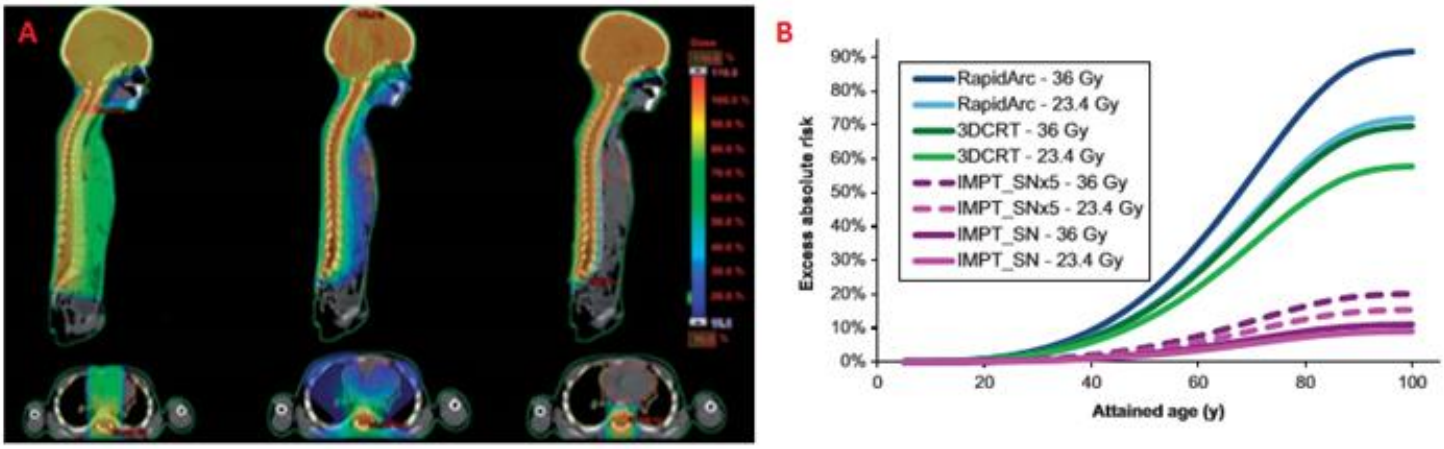

Figure 14: Image A depicts the dose distributions in the sagittal and transversal plane for treatment with 3D-CRT, arc therapy, and intensity modulated proton therapy (IMPT) (respectively, from left to right). Image B is the mean values for all 10 patients in the study of cumulative second cancer risk as a function of age for the three different treatment modalities studied. The results are given for two different dose levels for each treatment. The results are shown for the attained age up to 100 years, at which point the probability of living past this age (cancer or no cancer) is very low. Images adapted from Brodin et al.

The results from studies like the ones previously discussed have demonstrated that proton therapy reduces the predicted risk of second cancer when compared to intensity modulated radiation therapy and other forms of photon therapy such as 3D-CRT. In response to this knowledge, Rechner and colleagues studied whether this advantage persists when proton arc therapy is compared with volumetric modulated arc photon therapy. They compared the predicted risk of cancer following both of these treatment types for three prostate cancer patients. They analyzed the dosimetric data using five risk models and found the excess relative risk (ERR) of cancer in the bladder and rectum and calculated the ratios of these ERR values between proton arc therapy and VMAT. They even expanded their results to make direct comparisons with those from the Fontenot study discussed above[32].

Because rotational arc therapy distributes a lower dose over a larger volume of normal tissue than static beam radiotherapy, it cannot be assumed that the predicted risks of second cancer incidence in VMAT are comparable to those from IMRT and other static beam radiotherapy techniques. This was a primary motivation for Rechner and colleagues' choice of VMAT as a treatment type to study. The other motivation was the effectiveness and safety of proton arc therapy. Overall, they found that proton arc therapy significantly reduces the predicted risk of radiogenic second cancer in the bladder and rectum compared with VMAT. This was only true, however, in four of the five risk models. The linear-non-threshold risk model found no significant difference between the two. This slight discrepancy further highlights the need for many reliable risk models and the development of improved risk models. Overall, however, the results indicate that there is a difference between the two treatment techniques. The absolute individual risk of developing a second cancer from treatment was translated from their models to be about 1-2%. The best summary of the results from this study is in table 1 below where they compared their arc therapy ERR data with the ERR data from the Fontenot et

al. 2009 study comparing IMT with parallel-opposed beam proton therapy. ERR is the rate of cancer in exposed population relative to the rate of cancer in an unexposed population minus 1. They found that the risk of second cancer from therapeutic radiation following VMAT was less than that following IMRT and that the risk following parallel-opposed beam proton therapy was less than the risk following proton arc therapy (table 1).

Table 1: Predicted ERR values of second cancer incidence in the bladder, bladder wall, rectum, and rectal wall predicted with the LNT risk model from therapeutic radiation from IMRT, VMAT, lateral-opposed beam proton therapy, and proton arc therapy (PAT). The VMAT and proton arc therapy data came from the Rechner study and the IMRT and lateral-opposed proton data came from the 2009 Fontenot study. Table adapted from Rechner et al 2012.

	ERR			
Organ	IMRT	VMAT	Proton (lat-opposed)	PAT (uniform)
Bladder	8.88	5.25	3.68	4.86
Bladder wall	10.44	6.55	5.26	6.24
Rectum	3.32	2.09	2.01	2.74
Rectal wall	3.43	2.43	2.19	2.97

Interestingly enough, proton arc therapy has not yet been clinically implemented, but has been proposed. This paper suggests that proton arc therapy's implementation would be beneficial in terms of dose to healthy tissues and risk of second cancer. Future studies should look to investigate other aspects of proton arc therapy such as feasibility, cost of implementation, regularity, and other aspects of safety. The implementation of this technique seems promising and particularly intriguing to us. For that reason we included a discussion of it in the current review and suggest that this would be a valuable and exciting direction of focus for future research[30].

It is interesting to note that the body of research studying the risk of developing second cancers after radiation therapy treatment is based on predictions through risk models. It seems obvious to suggest that the field would benefit from a longitudinal study tracking actual individuals who have undergone each form of radiation therapy and recording the incidence of second cancers. This, however, would not work. The reason highlights the fascinating pace of the field of radiation therapy physics. A longitudinal study is useless because innovations in dose delivery are created so quickly that the clinical lifetime of a technique is far shorter than any longitudinal study. This makes it incredibly difficult to form a complete understanding of the risk of developing a second cancer. The field would benefit from increased attention to the development of more risk prediction models so that each body of results can be compared with several different models in order to shape a clearer picture of the probabilities.

3.4 Treatment Time

Treatment time also plays a role in the selection of therapy method. If a certain method takes too long, this may result in a treatment that raises the individual survival rate while sacrificing the population survival rate when fewer individuals can be treated. As a result, treatment time is an important consideration. We do not need to devote a detailed discussion to this topic, but a brief overview is important.

The use of VMRT over IMRT in recent years has grown due to its decreased dose to organs at risk and reduced treatment time[30]. The typical VMAT treatment period lasts 1-1.5 minutes where the typical IMRT treatment lasts 5-10 minutes[10]. In addition to this, the planning and quality assurance processes required for IMRT are more complicated, and as a result, time consuming compared with both VMRT and IMRT[10]. Image guided radiation therapy relies on time for imaging before and during the treatment process. This is one of the main drawbacks for IGRT – more time on the treatment couch and as a result, increased radiation delivered to the patient[10]. Because of its fast delivery time and low dose of radiation due to fewer monitor units, VMRT could maximize its potential through the incorporation of image guided radiotherapy. Where other modalities that take longer are made less useful by the incorporation of imaging, VMRT is fast enough that it could reasonable incorporate this extra dimension of treatment capacity. It is important to reiterate that when time is of the utmost importance and immediate delivery is required, the fastest treatment type is 2D-CRT, which is often used in these emergency cases[11]. Proton therapy is generally known to fall into the middle of the pack in terms of treatment time, and the proposed proton arc therapy, as discussed in the review of the Rechner paper, is expected to reduce treatment times even further[12].

3.5 Feasibility

The one result that is overwhelmingly persistent throughout the body of comparisons previously discussed is the strength of proton therapy. Until this point, it seems simple that the future lies in the proton therapy realm and appears as though it is silly to even consider photon therapy. All of this research and the body of promising proton results comes crashing down when feasibility is discussed.

Currently, there are only 25 cancer centers conducting proton therapy treatment in the United States. There are only 12 other centers that have proton therapy programs under construction. This means that in the near future, in order to receive proton therapy, one would most likely have to travel quite far and stay in hotels near a center for a prolonged period of time. This would mean missing work, being away from home, and an overall great deal of hassle and sacrifice. These clinics also have long wait lists so even if someone was open to this level of commitment, he or she may not be able to be treated.

The reason that there are so few proton therapy centers is that this treatment form is a great deal more expensive than any photon therapy treatment form. As of 2012, proton therapy required an investment of $100 million to $180 million[34,35]. The MD Anderson Cancer

Center reported that when patients of various insurance and payment plans are all considered, proton therapy delivery costs an average of $37,000 per patient for prostate treatment whereas IMRT costs $29,000 per patient and standard radiation treatment costs $21,000 per patient[34]. The cost differential in 2012 actually reflects a significant improvement over the last decade. In 2003, it was estimated that proton therapy was 2.4 times more expensive than photon therapy[36]. Proton therapy also requires the construction of an entire buildings to house the machines. They are extremely large and require three stories of building space and then additional treatment-associated areas[11]. This means that even if a cancer center has enough money to take on proton therapy, they may not have the space to do so. And of course, even if they have the space, the construction of a proton therapy building would require an investment of time and significant additional funds.

One of the most important advancements that can happen in the field of medical physics is the development of novel ways to bring down the costs of proton therapy. In this review we have come to the conclusion that proton therapy is often the best choice of treatment modalities. It is also, sometimes, the only choice. Photon therapy is incredibly ineffective in eye cancers. Currently, the most commonly employed option is complete eye removal. Studies, however, have shown that proton therapy can safely combat eye cancers. Studies as early as 1999 in France have demonstrated that proton therapy can fight cancer while also saving the eye and in a reported one third of cases, restore vision to useful levels[34]. This in itself seems to justify the need for increased feasibility of proton therapy.

The 2015 study by Newhauser and colleagues sought to investigate ways that the expenses associated with proton therapy can be minimized. They approached this by looking at collimators, range compensators, and hypofractionation. They suggested several cost-reducing modifications and tested their clinical strength compared with the typical proton therapy instruments. First, they replaced custom proton therapy fabricated collimators with a multileaf collimator. Next, they examined the impact of eliminating custom range compensators. They assessed these effects in 10 patients. They also assessed the risk of the development of second cancers after these modifications and examined the potential for hypofractionation, which is radiation therapy given in large doses over a shorter period of time than standard radiation therapy. They found that their adjustments had a negligible effect on the predicted dose distributions and the risk of developing a second cancer. Overall, their results showed that we are able to find ways to reduce treatment costs without sacrificing treatment quality[37].

4. Conclusion

The comparison in this review suggests that proton therapy is the best available treatment option for the majority of cases of cancer requiring radiation therapy. In each comparison outside of feasibility, including strength and effectiveness of treatment, dose delivered to healthy tissues, risk of negative side effects, and treatment time, proton therapy was found to be the best option. When feasibility is considered, however, proton therapy automatically drops to the least effective treatment because no matter how good it is, if people

cannot be treated by this method, it becomes useless. This means that we are essentially left with problems entirely within the control of the resources that we allocate to cancer treatment. With improved cost effectiveness or greater financial allocations to cancer treatment, and possibly the development of reduced machine size, we are on the brink of greatly improving cancer treatment. This, in combination with rapidly increasing innovations within the framework of available therapies, gives us great hope that we can continue to improve cancer care.

An interesting consequence of this body of research is that if proton therapy is not available, medical physicists are left with a complicated choice. We have seen that some forms arc therapy and IMRT lead to significantly higher chances of second cancer. On the other hand, 3D-CRT is likely to result in a variety of other very serious side effects such as heart failure and hearing loss. This highlights a very large hole in the body of medical physics research and an important future direction of study that results from all of the comparisons discussed in this paper. It is clear that if proton therapy is not available, there is a multitude of conflicting and confusing data in the photon therapy realm. One may be far superior at treating the cancer at hand while leading to the development of unwanted second cancers. Another may lead to a lower risk of second cancers but have a high risk of leading to heart failure and hearing loss. One form may be far faster than the others so that a greater proportion of the population can be treated, increasing population survival while potentially decreasing individual survival rates. As a result, there is a strong call for mathematical modeling of risk comparisons that can guide clinical decision making. If there is one takeaway from this analysis other than the strength of proton therapy, it is that the choice of treatment modality for a given cancer is a very complicated process. It is also a process where we would like to make absolutely sure that we have made the correct decision. The development of a mathematical model that can assess the clinical robustness and effectiveness of a treatment type for a given tumor type, size, and location while also taking into account the various secondary risks associated with treatment would be an absolutely critical advancement.

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