Radiation Therapy of Pediatric Brain Tumors: Comparison of Long-Term Health Effects and Costs between Proton Therapy and IMRT

by

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Submitted to the Engineering Systems Divisions and the Department of Nuclear Science and Engineering in partial fulfillment of the requirements for the degrees of

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Abstract

Radiation therapy is an important component of pediatric brain tumor treatment. However, radiation-induced damage can lead to adverse long-term health effects. Proton therapy has the ability to reduce the dose delivered to healthy tissue when compared to photon radiation therapy, but this dose benefit comes at a significantly higher initial cost, as proton therapy is 2 to 3 times more expensive to deliver than photon therapy.

This thesis provides a framework for the evaluation of health and cost effectiveness of proton therapy compared to Intensity Modulated Radiation Therapy (IMRT). Proton therapy and IMRT treatment plans of patients treated for low-grade gliomas (LGGs) were analyzed to provide risk estimates of long-term health effects based on the dose distributions. A Markov simulation model was developed to estimate the health effects and costs of proton therapy and IMRT. The model tracked a pediatric cohort treated for LGGs at age 5. In the model, the patients were at risk of acquiring IQ loss, growth hormone deficiency (GHD), hypothyroidism, hearing loss, and secondary cancer. Patients faced risks of death due to tumor recurrence, secondary cancer, and normal death. In addition, a review of literature was performed to estimate the costs and additional health risks not determined from the patient treatment plans.

The simulation results show that proton therapy can be cost effective in the treatment of LGGs based on the health risks estimated from the patients treatment plans. The cost associated with IQ loss and GHD were the main contributors to the total costs from long-term health effects. Proton therapy also results in a lower level of IQ loss and a lower risk of acquiring other long-term health effects. However, the relative difference in IQ point loss between the treatment modalities is small in the limited

number of patients studied. There is a need to further investigate the advantages of proton therapy in reducing the dose delivered to the relevant parts of the brain to lower the risks of adverse health effects, especially for IQ loss.

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I turned to Dr. Pamela McMahon at the MGH Institute of Technology Assessment for help with my model design. She has been an essential resource, teaching me the basics of technology assessment and how to work in TreeAge. She always made time to meet to discuss my model, and I walked away from our meetings feeling much more confident every time.

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One final comment: any mistakes in this document are solely my own and in no way a reflection of all the wonderful people who have helped me complete this thesis.

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Chapter 1

Introduction

Cancer is a leading cause of morbidity and mortality in the United States, accounting for nearly 1 in every 4 deaths. [1] In 2008, the cost of health expenditures for cancer care was $93.2 billion, accounting for roughly a third of the total health expenditure in the U.S. of $2.93 trillion [1] [2]. Radiation therapy is an important aspect of cancer treatment, used for approximately half of all cancer cases and often in conjunction with chemotherapy and surgery [3] [4]. Innovations in radiation therapy have led to more advanced radiation technologies, resulting in increased survival and improved quality of life for patients [5]. Proton radiotherapy and IMRT improve radiation therapy by targeting the dose to the tumor and minimizing the dose delivered to healthy tissue.

The support for proton therapy is based on the improvement in dose distribution that protons can provide [6]. Since radiation to healthy tissue is correlated with adverse health effects, treatment plans always aim to reduce radiation dose outside of the tumor volume. Due to their physical properties, protons are theoretically better able to target the tumor while significantly sparing healthy tissue compared to photons used in conventional radiation treatment.

The most advanced form of photon therapy is Intensity Modulated Radiation Therapy (IMRT). IMRT changes the fluence of the beams to target the tumor and spare the surrounding healthy tissue. [7] IMRT provides a high degree of control over the dose distribution to tumor and healthy tissue by modulating the intensity of the

photon beams, using cutting-edge optimization algorithms and multileaf collimators systems (MLCs) to shield and reduce the dose delivered to the tissue around the tumor.

Studies have shown that proton therapy spares more healthy tissue than IMRT during treatment. [8] [9] [10] However, proton therapy is more expensive than IMRT (estimates range from 30-500% more expensive), and questions remain regarding whether this cost is justified in terms of both short and long-term health improvements. [11] [12] Some state that proton therapy is projected to remain always more expensive than photon therapy, even with improvements in technology and learning. [12] Systematic reviews of the effectiveness of proton therapy in clinical practice point to the need for more research into the clinical and cost effectiveness of proton therapy. [13] [14] [15] After 30 years of proton therapy use, there appears to be no extensive randomized clinical evidence that protons provide better health outcomes than photons, except for ocular, brain, and pediatric tumors. [16] Even within the tumor types for which proton therapy is more effective, additional studies are needed to quantify the extent of the health and cost benefits.

This thesis addresses the need for evaluating the long-term health and cost effectiveness of proton therapy. The goals of this thesis are three-fold:

1. To provide a framework to estimate the long-term health effects and costs of proton therapy compared to IMRT.

2. To test if proton therapy reduces long-term health effects when compared to IMRT by analyzing patient treatment plans and modeling.

3. To determine whether the difference in risk of long-term health effects, calculated from the patient treatment plans dose-volume data, leads to an overall reduction in costs for proton therapy.

Since proton therapy is significantly more expensive than IMRT, questions remain regarding whether this cost is justified in pursuit of both short-term and long-term health improvements. The thesis addresses the following research questions:

1. Based on the difference in dose distribution between proton therapy and IMRT treatment plans, to what extent is proton therapy able to reduce the risk of adverse health effects?

2. Using the framework developed in this thesis, is proton therapy more cost-effective than IMRT for the treatment of pediatric low-grade gliomas when long-term morbidities are considered?

To limit the scope of this thesis, the assessment will be focused on the use of proton therapy for the treatment of pediatric brain tumors. Radiation therapy irradiates healthy brain tissue, and it is imperative to limit the dose delivered to the healthy brain to lower the risks of adverse health effects. Children are a particularly difficult population to treat as they are more sensitive to radiation and more likely to experience adverse health effects. [17] [18] The treatment of pediatric brain tumors using radiation can lead to severe health effects such as endocrine abnormalities, hindrance of growth, and impaired neuropsychological development. [17] [19] Since pediatric patients are likely to become long-term cancer survivors, post-treatment complications may be chronic and costly. As a positive correlation exists between adverse health effects and dose/volume delivered to healthy tissue, pediatric patients could potentially benefit from the improved dose distribution offered by proton therapy. [19] [20]

The target audience for this thesis is the four main stakeholders in the treatment of pediatric brain tumors using radiation therapy: patients, physicians, payers, and politicians. Patients are interested in receiving the best treatment available and will want to know what benefits in health effects can be expected from proton therapy. Payers (i.e. insurance, Medicaid, or out-of-pocket) and politicians will be interested in the cost-effectiveness analysis to determine whether proton therapy is a worthwhile investment. This thesis provides a framework for comparing proton therapy and IMRT to aid the stakeholders in deciding which treatment method is most appropriate.

Chapter 2 provides background information on the history and physics of proton therapy and IMRT. Chapter 3 provides a review of literature on the risk of the long-term health effects after radiation treatment for low-grade gliomas (LGGs). The

chapter focuses on IQ loss, growth hormone deficiency (GHD), hearing loss, hypothyroidism, and secondary cancer. Chapter 4 covers the methodology of the evaluation, detailing how the Markov model simulating two groups of patients treated with proton therapy and IMRT respectively was designed and how the risks and costs of each long-term health effect were determined . Chapter 4 also explains how the patient treatment plans were analyzed. Chapter 5 describes the estimated health effects from the treatment plan analysis and results of the model simulations based on the health parameters of each patient. Chapter 6 summarizes the results, pointing out the limitations of this framework and proposing areas for future work.

Chapter 2

Radiation Therapy Background

This chapter provides an overview of radiation therapy. A short history of radiation therapy is covered, with a focus on the development of proton therapy and IMRT. Section 2.2 discusses the differences between the two treatment modalities. Finally, a review of the physics and biology of radiation therapy is included.

2.1 History of Proton Beam Therapy and Intensity Modulated Radiation Therapy

Radiation therapy is a form of cancer treatment that uses radiation to destroy malignant cells, and proton beam therapy is a form of radiation therapy that uses protons. Physics research has led, directly and indirectly, to many advances in radiation therapy. With the discovery of x-rays in 1895 by Wilhelm Conrad Roentgen (who went on to win the Nobel Prize for his discovery), it was a matter of months before radiation began to be used as a cancer treatment. [21] In 1919, another Nobel Prize winner, Ernest Rutherford, showed the existence of protons by bombarding light elements with alpha particles, generating fast protons in the process. [22] This discovery, coupled with Ernest O. Lawrence's (also a Nobel prize winner) invention of the cyclotron - a machine able to accelerate charged particles to very high energies - in 1931, created the basis for proton beam therapy. [23] The theory of proton beam therapy was

developed in 1946 when physicist Robert Wilson published a study suggesting the potential benefits of protons in delivering a higher dose of radiation to the tumor while reducing the dose to the surrounding healthy tissue. Advances in imaging technologies in the 1980s allowed proton therapy (which requires precise location of the tumor) to become a viable treatment option.

The mid-20th century proved to be a productive time for cancer treatment, especially for radiation therapy. A particularly pivotal year was 1937, when cancer caught the American public's interest, with *Fortune*, *Life*, and *The New York Times* publishing articles and reports calling for a great need for action against cancer. [24] The U.S. Congress promptly passed the National Cancer Institute (NCI) Act on July 23, 1937, creating a new body to organize cancer research and education in the U.S. The first hospital-based clinical use of photon therapy was performed at University of California Berkeley (UC Berkeley) on a patient with leukemia. [23] UC Berkeley would also be the first to conduct animal and human proton therapy experiments in 1948 and 1954 respectively. After UC Berkeley's human trial in 1954, other institutions began to treat patients using proton therapy, including Harvard University led by a group from the Massachusetts General Hospital (MGH). [5]

Today, most radiation treatment occurs using high-energy x-ray beam (often referred to as photon beam), where photons are generated external to the patient and focused in a beam to target the tumor. [21] Intensity Modulated Radiation Therapy (IMRT) is the favored radiation treatment method using photons - according to a survey in 2004, 73% of responding U.S. radiation oncologists said they use IMRT. [25] As its name suggests, IMRT modulates the intensity of the radiation beams during treatment. These changes in the beam intensity create a treatment that manages "a higher degree of spatial agreement ('conformality') of the resulting dose distribution with the tumor target volume." In other words, the intensity of the photon beam is designed to be higher for the tumor volume and lower for the surrounding healthy tissue.

IMRT was first proposed in 1982 in a paper published by Anders Brahme et al, showing how to calculate a plan of non-uniform beams based on the desired dose

prescription - a process known as "inverse planning." [26] [21] Independently, Alan Cormack also proposed the idea that year, right after co-inventing the computed tomography (CT) scanner. The invention of the CT scanner played an important part in the development of IMRT, as advanced imaging techniques were necessary to detect the complex geometry of the tumor volumes and surrounding tissues.

Proton therapy, despite its late entry as a radiation-based treatment, is increasing the number of systems as demand quickly rises. As of 2008, nearly 20,000 patients have been treated with proton therapy in the U.S. and over 40,000 people treated worldwide. [27] [28] The number of proton therapy centers has quickly been growing. In the U.S., the first proton center was opened in 1991 at Loma Linda University Medical Center in California, followed a decade later by a flurry of proton center construction, starting with the Francis H. Burr Proton Therapy Center at MGH. [23] Currently, there are 29 proton centers operating around the world, and more are being built. [29] Proton therapy is used to treat a wide variety of tumors, including head and neck, pediatric tumors, ocular, lung, gastrointestinal, gynecological, bone and soft tissue, lymphoma, breast, and prostate tumors. [30] [31]

2.2 Proton Therapy Compared to IMRT

Radiation as a treatment tool is a double-edged sword: it effectively kills tumor cells but also damages healthy cells in the process. Since radiation to healthy tissue is correlated with adverse health effects, treatment plans always aim to improve tumor target and reduce radiation outside of the tumor volume. [32]

Proton therapy holds the promise of being a more effective radiation therapy than IMRT. Protons have the inherent physical properties of depositing most of their energy after traveling a well-defined distance. Protons can only travel a finite distance and deliver most of their energy at the end of their range - a phenomenon known as the Bragg peak (Figure 2-1).

Photon interactions occur based on a probability of interaction per distance, which depends on the target medium and photon energy. As photons travel through mat-

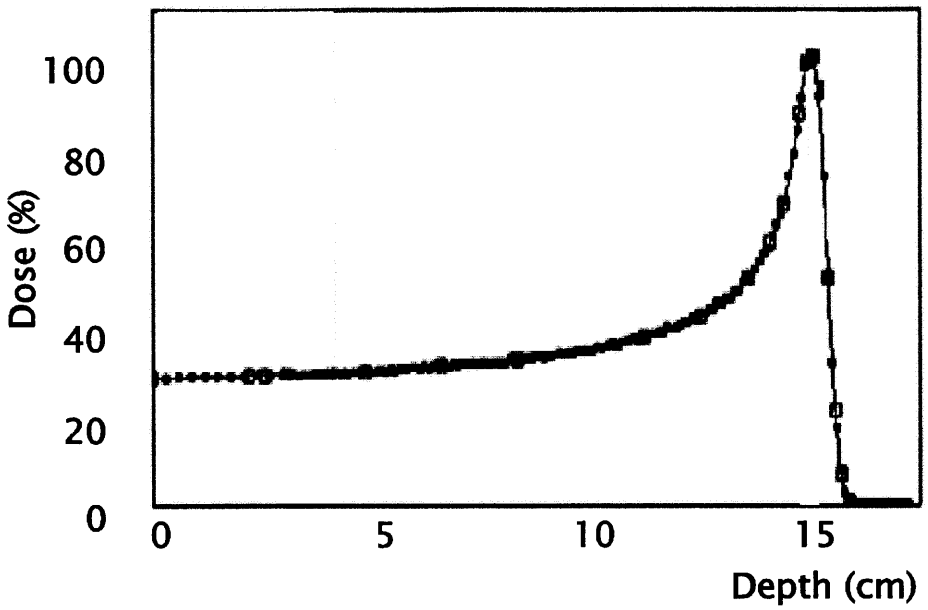


Figure 2-1: The Bragg peak, showing the finite range and location of peak energy deposition of protons in water. [21]

ter, they deliver the maximum dose near the beginning of their path and gradually attenuates. This attenuation gradually reduces the dose delivered as the number of photon decreases, as shown in Figure 2-2.

Since photons only gradually attenuates, they continue to deliver a dose beyond the tumor target, which is know as the exit dose. Protons are able to eliminate this exit dose as they have a sharp drop-off in their energy deposition at the end of their range. As shown in Figure 2-3, protons are able to deliver most of their energy within the target area (between the dashed green lines) and stop shortly after; photons, however, continue to deliver a dose beyond the tumor target. As the Bragg peak occurs at a narrow point, it is necessary in clinical practice to superimpose multiple Bragg peaks to give the appropriate dose to the target volume. This addition of multiple Bragg peaks creates a spread-out Bragg peak (SOBP), as shown in Figure 2-3.

A number of studies have been published comparing the dose-volume distribution of proton therapy and IMRT for solid pediatric brain tumors. [8] [9] [20] All the studies show that proton therapy spares more healthy tissue than IMRT and conventional

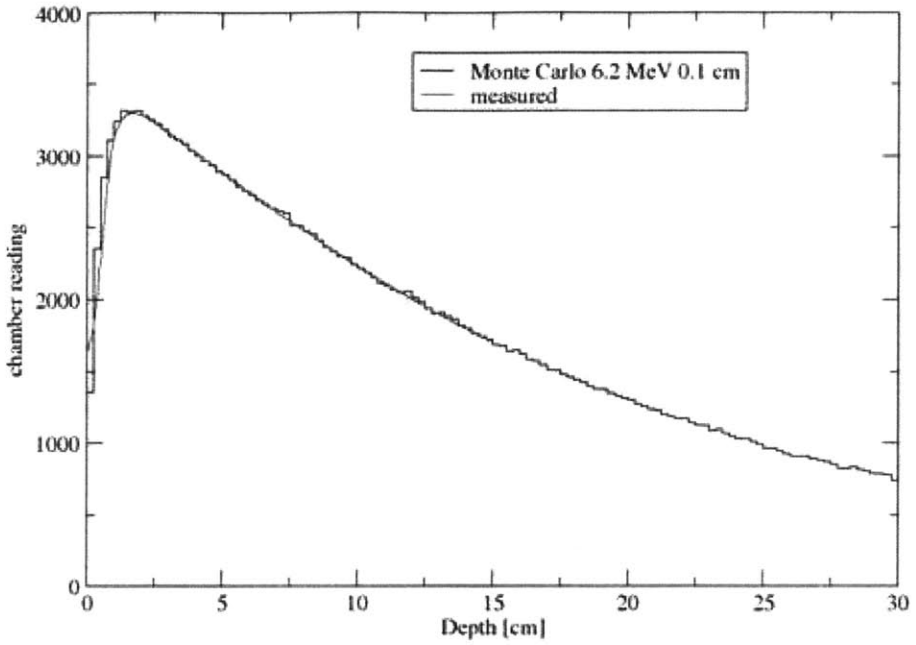


Figure 2-2: Attenuation of a 6 MeV photon through a water phantom, both simulated (Monte Carlo) and measured. [33]

photon therapy. A study published by St. Clair et al showed significant differences between proton therapy and photon treatment plans. In the case of medulloblastoma, a tumor in the posterior fossa, proton therapy is able to conform to the relevant body part and avoid irradiating other volumes. Medulloblastoma treatment requires irradiation of the entire spinal cord, which results in irradiation of the chest area when using photons. Figure 2-4 shows an image of the percent of full dose delivered to the spinal cord and chest, with proton therapy significantly sparing the chest, avoiding dose to critical organs.

Proton therapy is most promising in reducing the risks of adverse health effects for the treatment of pediatric tumors. Children diagnosed with cancers today have over an 80% chance of 5-yr survival. [34] [35] [36] Cancer survivors may suffer from a range of adverse health effects associated with the treatment of the primary tumor. [32] The need to reduce the dose delivered to normal tissue is especially imperative when treating children who are more sensitive to radiation and who live longer with adverse health effects than adults. [10] [37] A few studies have indicated that the differences

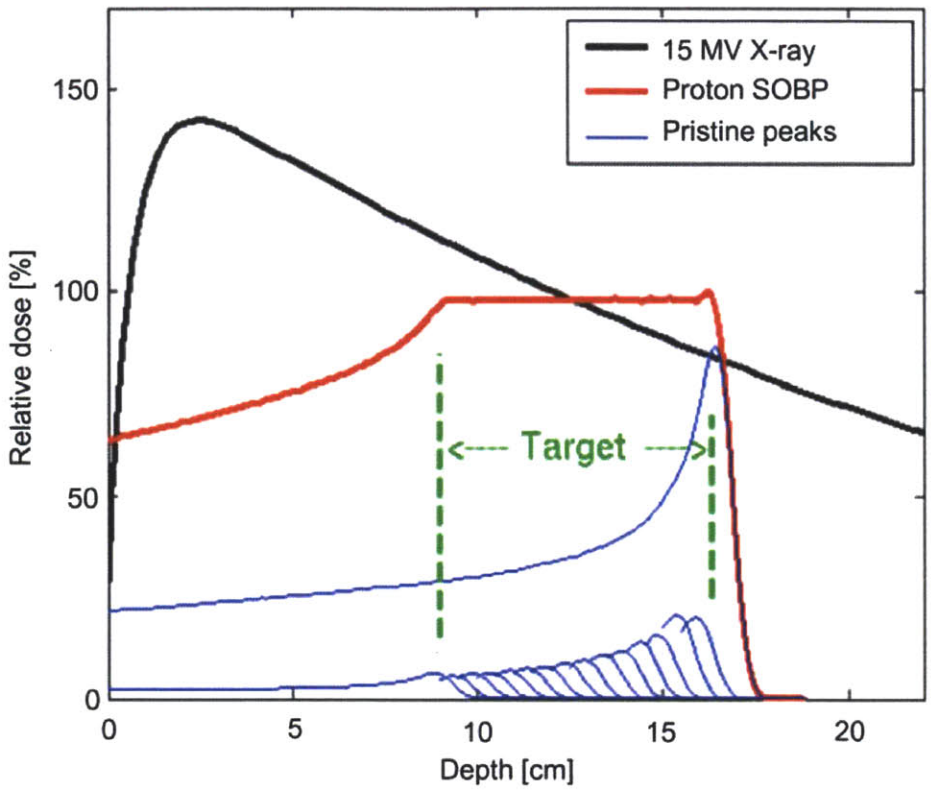


Figure 2-3: Comparison of the dose deposition between protons and photons in tissue. The black line represents a 15 MeV photon beam, the blue lines repesent multiple Bragg peaks that make up the spread-out Bragg peak (red line). The dashed green line delineates the tumor target. [21]

in dose distribution between proton therapy and IMRT can result in a lower incidence of common pediatric late health effects. [20] [38] [39] Even though proton therapy has demonstrated its potential in reducing the radiation dose delivered to healthy tissue, there is still a dearth of data on clinical evidence indicating health benefits from proton therapy compared to IMRT. [14] [15] In part, this is because proton therapy there ha been a lack of randomized clinical, and those studies are slowly starting to appear. Another reason is that it is difficult to have long-term comprehensive follow-ups with patients who come from all over the country to be treated and do not return afterwards. [40]

It is also not always the case that proton therapy results in a clinically significant improved dose distribution compared to IMRT. Looking at Figure **??**, proton therapy

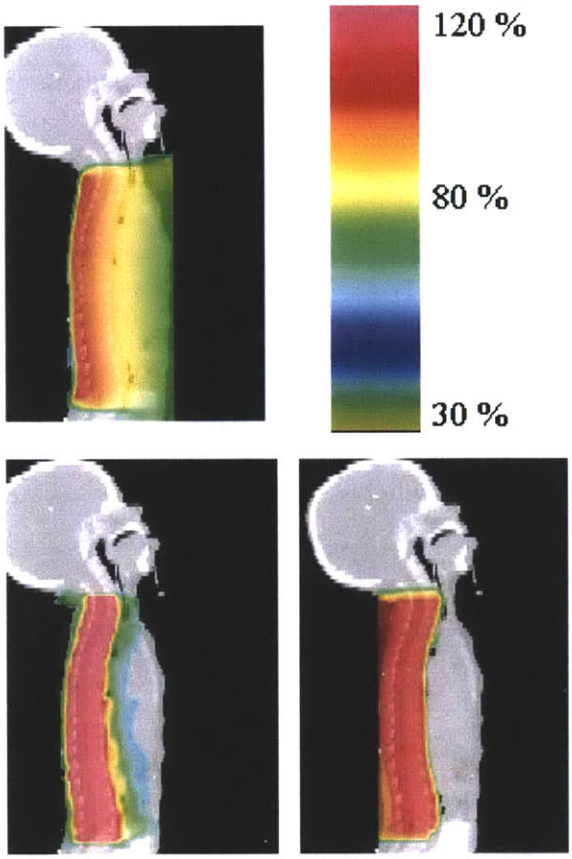


Figure 2-4: Dose distribution along the spinal column of a child treated with coventional X-rays (top left), IMRT (bottom left), and protons (bottom right). Significantly lower doses are delilivered to the torso when treating with proton therapy compared to conventional x-rays and IMRT. [8]

is a clear improvement over conventional photon therapy treatment, but the difference between IMRT and proton therapy is not as pronounced. Follow-up studies of patients who have been treated with proton therapy seem to indicate that protons do lead to a lower risk of side effects in certain situations - but not all. For example, a recent study by Winkfield et al found that the risk of getting a secondary cancer from proton therapy can be higher than from IMRT depending on the number of fields used. To reduce the total dose that each beam delivers to a particular area, the number of beams used is increased; however, this results in more healthy tissue being irradiated, which could explain the increased secondary cancer incidence.

In the face of the paucity of randomized clinical data, this thesis aims to evaluate

the extent to which differences in health effects can be expected based on the dose distribution from actual proton therapy and IMRT treatment plans. Models have been developed to quantify the dose-volume effects of radiation on risk of adverse health events from the follow up of patients treated with photon radiation. Merchant *et al* developed models that relate dose to magnitude of IQ loss and GHD. [41] [42] [43] The risk of hearing loss was found to increase based on the mean dose delivered to the cochlea. [44] Furthermore, each one of these morbidites have a cost associated to it. This thesis provides a model to determine whether proton therapy is effective in reducing the incidence of health effects and their associated costs.

2.3 Radiation Physics and Biology of Radiation Therapy

The information in this section is primarily drawn from the books by Turner and Goitein, unless otherwise noted. [45] [21]

2.3.1 Photons

Photons are light particles and have neither electric charge nor actual mass. They can be referred to as gamma rays or x-rays, based on their origin. Gamma rays come from atoms with an excited nuclear state, causing the nucleus to release its excess energy in the form of photons to reach a stable state in a process known as gamma decay. As Roentgen discovered in his cathode ray experiment, x-rays are generated when electrons are sent towards a heavy target (i.e. target made of atoms with a high atomic number). Those electrons collide with other electrons in the target or be deflected from their course as they pass near the positively charged nuclei, losing energy by releasing an x-ray photon. This creation of a photon by particle deceleration is known as bremsstrahlung, which comes from the German words for 'to brake' (bremsen) and 'radiation' (Strahlung). [46] In this thesis, x-rays will be referred to as photons unless otherwise specified.

2.3.2 Protons and the Bragg Peak

Protons are positively charged particles that interact with matter via two main types of interactions: Coulombic interactions (with atomic nucleus and electrons) and nuclear interactions with the atomic nucleus. As a proton traverses a medium, it can attract electrons away from atoms, ionizing the atom and setting electrons loose. Protons do not lose much energy during a Coulombic interaction with electrons and will experience, on average, hundreds of thousands such interactions per centimer traversed. Since protons are 1836 times heavier than electrons, they barely experience any deflection from their path. However, protons will experience a repulsive force when passing near the atomic nucleus, which is positively charged. Since the atomic nucleus is usually heavier than a single proton, the nucleus will deflect the proton (albeit, at a small angle).

The Bragg Peak is a result of proton's Coulombic and nuclear interactions. Protons slowly lose their energy through thousands of Coulombic interactions with electrons, but this energy loss varies as protons travel through matter. Like all heavy charged particles, protons lose their energy as defined by the Bethe-Bloch stopping-power formula. As protons slow down, tehy transfer more energy during each collision, resulting in a peak rate of energy loss near the end of their trajectory, as indicated in Figure 2-1.

2.3.3 DNA Damage

Radiation damages a cell by breaking bonds in DNA, effectively killing the cell or stopping the cell's ability to reproduce. As radiation travels through the body, it interacts by ionizing the particles in the cell - particularly water molecules (~70-85% of the makeup of human cells). Radiation can affect a cell's biology directly and indirectly. For example, a direct effect can result from the radiation ionizing atoms in the DNA helix, breaking the DNA bonds. Radiation can generate indirect effects by forming free radicals (i.e. particles with unpaired electrons, such as H_2O^+ and H) or other byproducts. These byproducts can subsequently interact with DNA, such as

a free radical reacting with DNA sugars and resulting in a stand break.

Tumor and healthy cells respond differently to radiation interactions. Tumor cells tend to be more susceptible to radiation damage, likely due to their genetic makeup - though this phenomenon is currently not completely understood. This phenomenon is especially useful when healthy cells are found within the tumor or nearby but are included in the target volume.

2.3.4 Radiation Dose

Dose delivered to a patient is measured in terms of Gray (Gy). A Gray represents the energy from radiation absorbed per unit mass, where:

$$1 \text{ Gy} = 1 \text{ J/kg}$$

Radiation therapy can deliver doses up to 60 Gy to certain parts of the body. An acute delivery of the full dose (on average around 50 Gy, though greatly depends on tumor) required to destroy a tumor could kill the patient if delivered acutely to the whole body or critical organs. Hence, fractionation is an extremely important aspect of radiation treatment. A treatment plan will conventionally be broken up into 2 Gy fractions delivered once a day, with a break over the weekend.

2.3.5 Relative Biological Effectiveness

The effectiveness of different types of radiation is compared using their relative biological effectiveness (RBE). RBE is defined as ratio of the x-ray dose compared to dose of another radiation type required to produce the same specific biological end point (e.g. level of tumor cell deaths). RBE is determined by:

$$\text{RBE} = \frac{D_{\text{x-ray}}}{D}$$

where D is the dose of a type of radiation that produces a particular biological end point and Dx-ray is the x-ray dose needed to reproduce that end point.

Protons are generally accepted of as having an average RBE of 1.1, meaning that it would require about 10% more x-ray dose to reach the same biological end point as protons.

Based on the physical properties of protons, proton therapy can significantly reduce the dose delivered to healthy tissue. This benefit is especially important when treating pediatric patients who are not fully developed and are more sensitive to radiation damage. The next chapter discusses the health risks associated with childhood brain tumor survival, with a focus on the effect of radiation on those risks.

Chapter 3

Pediatric Low-Grade Gliomas and Long-Term Health Effects

Gliomas are tumors of the central nervous system (CNS), which consists of the brain and spinal cord. CNS tumors are the second most common tumors in children after hematological malignancies. [47] Every year, about 43,800 cases of brain tumors are newly diagnosed in the U.S. Roughly 3,000-4,000 of those cases are pediatric brain tumors. Low-grade gliomas (LGGs) are the most common form of pediatric brain tumors, accounting for roughly 50% of all cases. [48] LGGs are generally slow growing and benign tumors, thus increasing the chance of survival. LGGs are usually treated with surgery (resection of some or all of the tumor volume), chemotherapy, radiation therapy, or a combination of the three. [49] [50] Most LGG patients will require radiation therapy, especially for centrally located tumors that cannot be removed by surgery. [42]

The advantages of more precise radiation therapy are especially important for pediatric LGG survivors. Children treated for LGG are most likely to survive compared to the population treated for all brain tumors, with 10-20 year survival rates well above 80%. [48] [51] [52] Since many children with LGG will become long-term survivors, they are likely to experience a number of adverse health effects after treatment. Children who survive brain tumors are especially susceptible to long-term morbidities as children's brains are not fully developed by the time of disease onset

and treatment. [47] The main health effects of concern from radiation treatment are neurocognitive, endocrine, and ototoxicity disorders, and secondary cancer. [52] [42]

3.1 Neurocognitive Dysfunction

Partial to full irradiation of the brain can result in multiple, long-term neurocognitive effects such as attention, memory, language, and executive function deficits. [53] [54] Intelligence Quotient (IQ) has been used as a benchmark to quantify the extent of neurocognitive damage. IQ is a score generated from tests designed to assess intelligence. Pediatric patients who receive radiation treatment are likely to experience IQ loss, with IQ changes greater than 10%. [41] [55] The relationship between radiation dose to the brain and IQ loss is not fully understood, though it is generally accepted that a higher dose to the brain will result in a higher level of IQ loss. [50]

Fuss *et al* performed a systemic review of 36 publications on neuropsychological impairments from children treated with radiation. [56] The data from the publications represents 1,938 children and examines radiation dose, irradiated volume, and age. Doses greater than 24 Gy resulted in IQ loss. Age was a clear factor in IQ score, with children under the age of 3 receiving doses higher than 24 Gy having lower than normal IQ scores (less than 85 points); while children older than 6 experienced that level of IQ deficiency when receiving doses higher than 36 Gy.

Researchers at St. Jude Children's Research Hospital have published various studies that investigated the dose-volume effect of radiation on the magnitude of IQ loss. [41] [51] Merchant *et al* found mathematical relationships between dose to brain and IQ loss from studies of pediatric patients with LGGs. The group developed different IQ loss models for specific brain tumors: all LGGs, craniopharyngomas (CR), ependymomas, and medulloblastomas (MB). Merchant *et al* chose those specific tumors due to their different locations in the brain: ependymomas and MBs can be found in the infratentorial region; LGGs and CRs can be found in the supratentorial region, closer to critical structures such as the left temporal lobe, puitary glands and hypothalamus. [20]

For all LGGs, the study analyzed a group of 78 pediatric patients treated with 54 Gy of CRT between August 1997 and August 2006. [42] Merchant *et al* found that a patient's IQ loss was dependent on the dose-volume distribution given to the supratentorial brain (the top area of the brain, consisting of all brain except for the posterior fossa) and age at radiation treatment, as shown in Equation 3.1:

$$\text{IQ} = 95.5545 + \text{Age} \times 0.3291 + \text{Time} \times (\text{Age} \times 0.00273 - V_{0-30} \times 0.0027 - V_{30-60} \times 0.0047) \tag{3.1}$$

where Age is the age in years when patient receive radiation treatment, Time is the time in months since radiation treatment, V_{0-30} is the percentage of supratentorial brain that received 0 to 30 Gy, and V_{30-60} is the percentage of supratentorial brain that received 30 to 60 Gy. The more volume of the supratentorial brain that received a high dose (30-60 Gy) resulted in a higher overall IQ loss. Age at time of treatment was also a factor that influenced the magnitude of IQ loss (i.e. worse for younger patient).

For ependymomas, the study followed 88 patients who received 54-59.4 Gy during radiation treatment from July 1997 to January 2003. The group found an estimation equation for the dose to the supratentorial brain. [41] The MB and CR models were less detailed, only using the mean dose to the supratentorial brain to estimate IQ. [20]

The analysis of Merchant *et al*'s studies led to two points of confusion. The first is that the standard errors to the IQ loss are poorly defined (if at all). Specifically, it is not clear if all patients should expect IQ loss based on his mathematical models or not. Second, his study for IQ loss after CRT for enpendymoma provides multiple mathematical models, correlating IQ loss with dose to the whole brain, left temperoral lobe, and supratentorial lobe individually. Testing of those equations with data from the treatment plan used in this thesis of a patient with an ependymoma provide different values for IQ loss depending on the brain structure.

Ultimately, it is unclear if dose to the supratentorial brain is solely responsible for IQ loss as other studies show IQ loss related to dose to other parts of the brain. Jalali *et al* found a significant difference in the risk of obtaining a high IQ loss (greater than

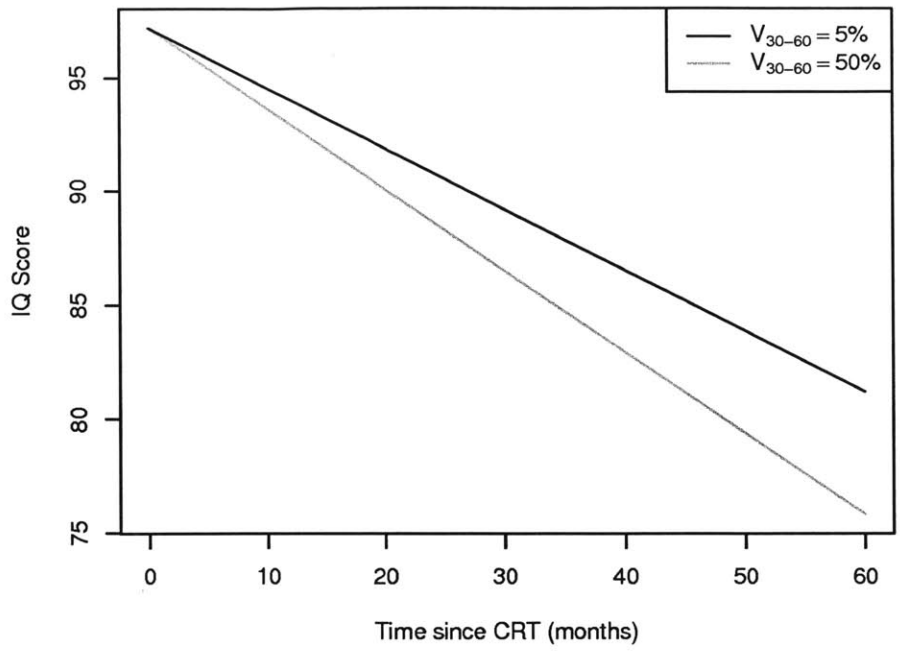


Figure 3-1: IQ loss comparison based on dose to the supratentorial brain. Significant difference in IQ loss can be expected for patients treated with a higher dose to the supratentorial brain. This graph was generated using the dose-IQ relation developed by Merchant *et al.* [51]

10 points) if at least 13% of the left temporal lobe received 43.2 Gy or higher. Other studies have analyzed the loss of normal white matter and found a correlation with neurocognitive defects. [52] [54] Nevertheless, the Merchant *et al* studies are currently the only studies that mathematically model IQ loss based on dose to the brain. As proton therapy has the ability to deliver less high doses to the supratentorial brain during treatment, it would be expected that significant differences in IQ loss would be found between proton therapy and IMRT.

3.2 Endocrine Dysfunction

Endocrine complications occur from damage to the hypothalamus and pituitary gland, which disrupts regular hormone release. Two common endocrine complications of brain tumor survivors are growth hormone deficiency (GHD) and hypothyroidism.

GHD is usually caused by the loss of the growth hormone-releasing hormone neu-

rons in the hypothalamus. [43] The reports of GHD incidence varies from study to study, based on the tumor type and the number of patients available for analysis. Incidence of endocrine dysfunctions will be as high as 83% for a pediatric LGG population, with the majority from GHD. [52] A study from St.Jude Children's Research Hospital (n= 78) found a 10-year cumulative rate of GHD at 49% for LGG pediatric patients treated with photons. [51]

Growth hormone therapy is usually stopped once children reach their final height. [57] However, it does not necessarily mean that the patient is no longer growth hormone deficient. Gleeson *et al* tested a group of 73 children about 10 years after radiation therapy, at an average age of 15 years, which is usually when growth hormone treatment is stopped. [58] All the children were on growth hormone replacement for severe or moderate GHD. The study found that ~50% of the pediatric cohort with GHD after radiation treatment tested positive again for GHD at final height. A similar study by Gurney *et al* found that close to 40% of the childhood brain cancer survivors were below the 10th percentile for height. The Gurney *et al* study was part of the Childhood Cancer Survivor Study and was able to draw data from 921 young adult survivors of brain cancer.

Hypothyroidism is a condition in which the thyroid does not produce a sufficient level of hormones. [59] Thyroid hormones are crucial in regulating the body's metabolism, temperature, heart rate, protein production, and calcium in the blood. The hypothalamus and pituitary glands control the rate at which thyroid hormones are released, and hence any damage caused by radiation can result in disruption in the thyroid hormone release. The same LGG study from St.Jude Children's Research Hospital found a 10-year cumulative incidence of hypothyroidism at 68%. [51] Their findings were aligned with the findings by Rose et al reporting 69% of patients with brain or nasopharyngeal tumors with hypothyroidism. [60] No studies so far have attempted to model the correlation between dose and level of thyroid hormone deficiency.

Other endocrine dysfunctions, such as diabetes, delayed or early onset of puberty, and testosterone deficiency, were not explored in this study. These deficiencies have

been noted but have not been studied as completely; therefore, the risks of those health-effects were not considered in this thesis.

3.3 Hearing Loss

Hearing loss is a common side effect in patients treated with radiation for brain, head, and neck tumors. [44] [61] The onset of hearing loss usually occurs when the cochlea receives high doses of radiation, in excess of 30 Gy. [42] The area that translates high frequencies (4000-8000 Hz) is more sensitive to radiation than other parts in the cochlea. High frequencies are crucial in the understanding of speech, with 50% of English sounds at energy frequencies up to 8000 Hz. [61]

The threshold for hearing loss for children is between 35-45 Gy. [44] [62] Chiaho Hua *et al* reported a hearing loss rate of 14% from a study of 78 patients with localized brain tumors followed 3-5 years after radiation treatment. [44] Hearing loss incidence increased for doses greater than 40Gy, with a higher risk of loss at higher frequencies (6000-8000 Hz). The study found that the onset of hearing loss occurred 3-5 years post treatment for 75% of the cases, though hearing loss can occur as early as 2 years after treatment. Median hearing loss onset is 3.5 years post treatment.

A group at Texas Children's Hospital investigated the onset of hearing loss in 44 pediatric patients treated for medulloblastoma from 1998 to 2006 using IMRT. [62] The median follow-up time was 41 months. They found that 25% of the children experienced high frequency hearing loss, with the higher mean dose to the cochlea increasing the severity of the hearing loss.

Merchant *et al*'s follow-up of 78 pediatric patients with LGG found that doses greater than 45 Gy resulted in significantly higher risk of high frequency hearing loss. For 6000 and 8000 Hz frequencies, the risk of hearing loss at doses greater than 45 Gy was 19.2% each compared to 0% at less than 45Gy. The group only found a correlation between dose to the cochlea and hearing loss in the right ear. There are multiple other factors that could be associated with hearing loss, such as genetic make-up and chemotherapy; however dose to the cochlea still remains the

main factor. [44]

3.4 Secondary Cancer

Currently in the United States, about 10% of cancer patients are treated for a secondary malignancy. [37] Secondary cancer is the onset of another malignancy after the treatment of the primary tumor. The risk of secondary cancer is associated with genetic make-up, type of primary tumor, and treatment method. [39] [63] Children are especially susceptible to secondary cancers for three reasons: [37]

1. They are 10 times more sensitive to radiation than adults. Studies of the Japanese atomic-bomb survivors show an increased risk of radiation-induced cancer at a younger age.

2. Any radiation scatter is more likely to deliver a higher dose to critical organs than for adults, as shown in Figure 3-2.

3. Children with primary cancers are likely to have genetic mutations that make them more prone to radiation-induced cancers. For example, children treated with radiation for Hodgins disease were had a higher risk of breast cancer than children treated for other tumors. [?] However, the general understanding of genetic susceptibility is still unclear and requires further study.

The most extensive secondary cancer study has been the Childhood Cancer Survivor Study (CCSS). [64] [65] CCSS is a large retrospective study of over 14,000 childhood cancer survivors. The follow-up period of the patients is the longest to date: 25-30 years after treatment of the primary tumor. The patients included in the study survived for at least 5 years after treatment. The study analyzed the incidences of secondary cancer based on many different criteria, such as gender, age at diagnosis, primary tumor diagnosis, and primary tumor treatment. The cumulative 30-year incidence of secondary cancer was 9.3% . [64] Female survivors were 1.64 times more likely to develop a secondary cancer than male survivors. Radiation therapy increased the risk of secondary cancer, especially if the patient was treated for the

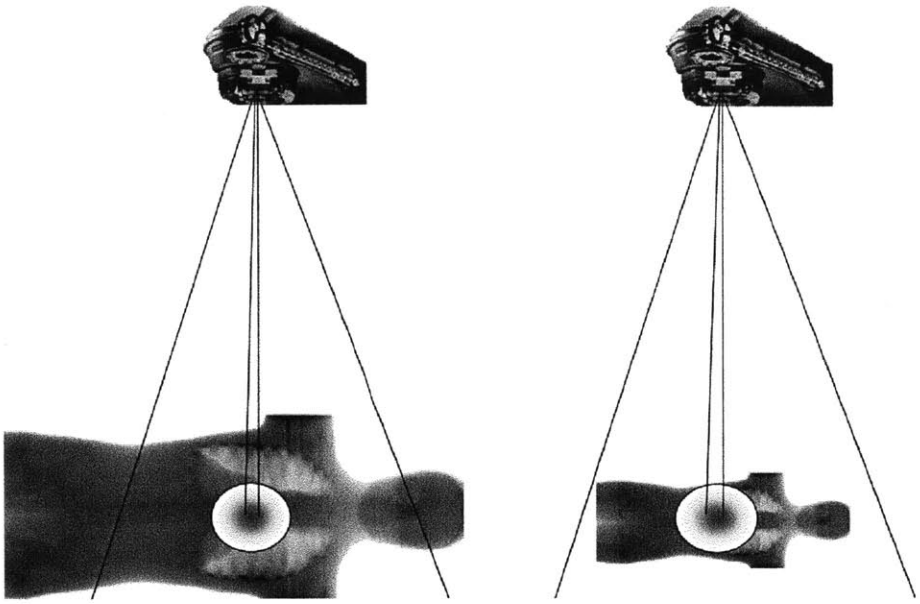


Figure 3-2: Comparison of scattered dose to body when treating an adult (left) and a small child (right).[37] A more significant volume of the child's body is irradiated compared to the adult's irradiated volume for the treatment of a similar tumor volume.

primary tumor at a younger age. A more focused analysis of the CCSS found that patients treated with radiation therapy were more likely to develop a secondary CNS cancer. [65]

Researchers at St. Jude Children's Research Hospital performed a study on a cohort of 1,283 patients treated for pediatric CNS tumors between January 1984 and January 2002. [66] The patients were all under 22 years at time of treatment. The study found that the 14-year cumulative incidence of secondary cancer was 5.3% (95% CI, 2.0-8.5%). The 10-yr estimated cumulative incidence of second malignant neoplasms for patients with LGGs was 0.4% (95% CI, 0-0.8%). All the patients with a secondary cancer from LGGs (n=10) were treated with radiation therapy for the primary tumor and received on average 50 Gy at the site where the second tumor appeared. However, the study was unable to parse out the effect of chemotherapy and radiation therapy on the risk of secondary cancer.

Recent studies have modeled the risks of secondary cancer from proton therapy and IMRT. Mu *et al* compared treatment plans for medulloblastoma based on

IMRT, intensity modulated proton therapy (IMPT), conventional electron therapy, and intensity-modulated electron therapy (IMET).?? IMPT differs from proton therapy in that it utilizes magnetically scanned pencil beams that specifically conform to the target volume. [7] Conventional proton therapy uses broad proton beams that are molded to the patient by using specially designed apertures and compensators for each patient - a process known as passive scattering. The group found that IMRT had the highest risk of secondary cancer (30%) and IMPT had the lowest risk (4%). However, IMPT is not currently the main form of proton therapy treatment as most facilities use the passive scattering technique. It is expected that the risk of secondary cancer from proton therapy is higher than the risk from IMPT.

Miralbell *et al* and Winkfield *et al* also analyzed the risk of secondary cancer from proton therapy. [39] [67] The Miralbell *et al* study designed treatment plan for two cases of pediatric brain tumors: parameningeal rhabdomynsarcoma (RMS) and MB. [39] Using the dose-volume histograms generated from the treatment plans, they estimated a yearly risk of secondary cancer risk for IMRT and proton therapy at 0.43% and 0.05% respectively for MB. The yearly risk for RMS was 0.05% for IMRT and 0.04% for proton therapy. The risk of secondary cancer from MB treatment is expected to be higher than for RMS treatment as the whole brain and spinal cord are irradiated. Only the tumor volume is targeted in radiation treatment of RMS.

The Winkfield *et al* study estimated the risk of secondary cancer for adults treated for pituitary adenoma. [67] They compared IMRT and proton treatment plans with different numbers of treatment fields. The overall excess number of secondary cancer cases was 25 per 10,000 patients treated with IMRT and 20.4 per 10,000 patients treated with proton therapy. However, they found that proton therapy would cause a higher excess risk of secondary tumor if the treatment plan called for more than two fields. Namely, 2-field IMRT treatment resulted in a 9.8 per 10,000 patients excess risk, compared to 12, 15, and 16 per 10,000 patients for 3-field, 4-field, and 5-field proton therapy treatment respectively.

The largest clinical study so far investigating the risk of secondary cancer from proton therapy was conducted at the Massachusetts General Hospital (MGH). [68]

Preliminary and as of yet unpublished results from this study found that the incidence of secondary cancer 15 years after treatment was 7% for proton therapy and 20% for photon therapy. [68] The study followed a group of 488 proton patients and 488 photon patients, treated for all types of tumors. Patients had a median age of 56 years for the proton cohort and 59 years for the photon cohort, though both cohorts included pediatric patients. The study adjusted for gender and age at treatment.

3.5 Cost-Effectiveness Analysis of Proton Therapy for the Treatment of Pediatric Tumors

There are currently only a few published studies that investigate the cost-effectiveness of proton therapy compared to conventional photon therapy and/or IMRT. [19] [69] [70] The study most relevant for the work in this thesis is Lundkvist *et al*'s cost-effectiveness analysis of proton therapy for the treatment of pediatric medulloblastoma. [19] The group designed a Markov model to simulate two groups of children receiving proton therapy or conventional photon therapy in Sweden. Their model included seven types of long-term health effects: hearing loss, IQ loss, hypothyroidism, GHD, osteoporosis, cardiac disease, and secondary cancer. Lundkvist *et al* estimated the risks of healths effects based on a review of literature and the costs were estimated for a Swedish pediatric population. Their model found that proton therapy resulted in €23,600 in cost savings. IQ loss and GHD were the main contributors to the cost savings.

The model in this thesis updates the work by Lundkvist *et al* by estimating the risk of long-term health effects from the analysis of patient treatment plans, using existing models that relate dose to risk of health effects. Results of more recent clinical studies of pediatric proton patients are also used. Furthermore, the costs in this model are updated to apply to a U.S. pediatric population. The next chapter describes the treatment plan analysis and model design in detail.

Chapter 4

Methodology

This chapter explains the method applied to evaluate the health effects and costs of proton therapy and IMRT. The analysis involved a four-step process (Figure 4-1):

1. Literature review and MGH staff interviews.

2. Analysis of patient treatment plans.

3. Estimation of risks and costs of long-term health effects.

4. Design of a Markov model to simulate pediatric populations treated for LGGs with proton therapy and IMRT.

The findings of the literature review and MGH staff interviews were described in Chapter 3. This chapter explains how process 2 through 4 were accomplished. The first section details how proton and IMRT treatment plans from pediatric LGG patients were collected and analyzed to determine the risks of IQ loss and hearing loss. A Markov model was designed to determine the long-term health effects and costs that are incurred by pediatric LGG survivors throughout their lifetime. The Markov model was evaluated as a Monte Carlo simulation to determine the prognoses of a large number of individual patients. Section 4.2 describes the model in details, explaining how the health risks and their associated costs were determined and applied.

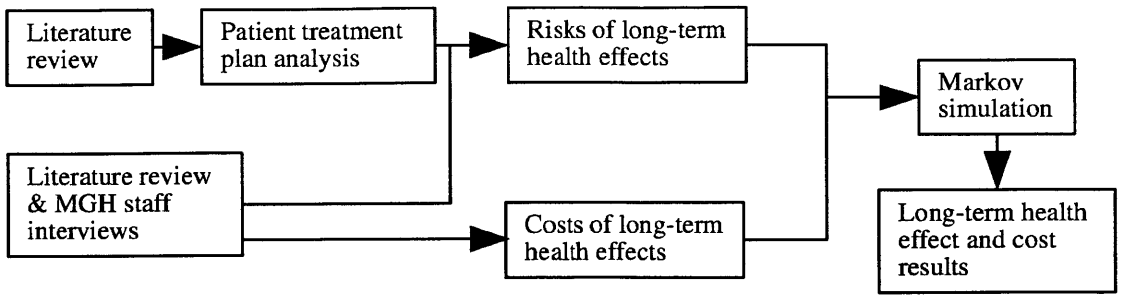


Figure 4-1: Flow chart of the methods applied in the analysis of the long-term health effects and costs of proton therapy and IMRT

4.1 Patient Treatment Plans

Four patient treatment plans were obtained from the Massachusetts General Hospital (MGH) for analysis. The patients were chosen based on two criteria:

1. Pediatric patient diagnosed with LGG.

2. Both proton therapy and IMRT treatment plans were designed for each patient.

The treatment plans from two of the patients were used for the full analysis, while the other two were used only for further IQ change analysis. The two patients used for the full analysis were the only cases that had both IMRT and proton plans with all of the necessary brain structures outlined. In this document, they are referred to as P1 and P2. P1 was a female patient age 8 with a pilocytic astrocytoma. P2 was a female patient age 5 with a posterior fossa ependymoma. Two more patient treatment plans were added after initial analysis of the results to investigate further the difference in IQ loss between proton therapy and IMRT. P3 was a male patient age 7 with a craniopharyngioma. P4 was a male patient age 14 with a LGG. All of the patients were treated at the Francis H. Burr Proton Therapy Center at MGH using a 240 MeV cyclotron.

Patients were treated according to a Local Protocol #10-206, developed at MGH as part of a follow-up study of patients treated for pediatric brain tumors using proton therapy to determine their long-term health effects. [71] For LGG, a dose of 50.4-54 Gy was delivered to the tumor volume. The full dose was delivered in 1.5-2.0 Gy

fractions (typically 1.8 Gy/fraction), 5 days per week.

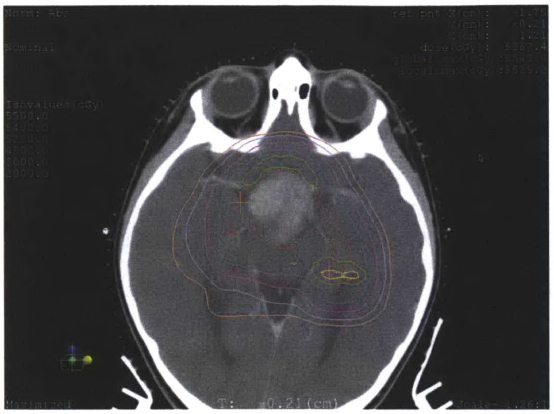
The treatment plans were developed using XiO® treatment planning software. The gross target volume (GTV) was defined as any gross disease visible on the MRI. The clinical target volume (CTV) was defined as a 3-7.5 mm expansion of the tumor, based on the physician's judgment of the extent of microscopic disease. Figure 4-2 shows images generated in XiO® from P1's treatment plans. The XiO® images for P1 and P2 are available in Appendix A. The red line represents the contour of the tumor volume. All the other contour lines are isodose lines that indicate which volume of the brain received the associated dose level. For example, any volume inside of the magenta isodose line received 4,500 cGy or higher in the proton treatment plan and 4,000 cGy or higher in the IMRT treatment plan shown in Figure 4-2.

4.1.1 Dose-Volume Histograms

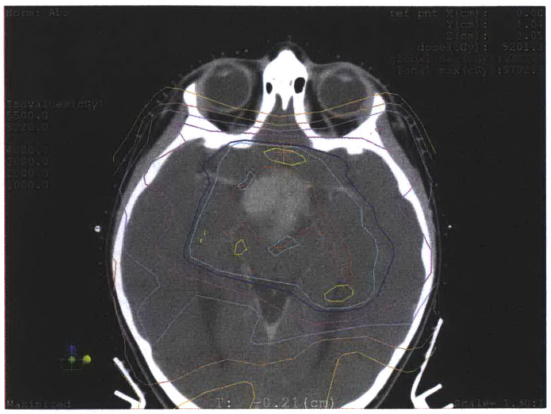
Dose-Volume Histograms (DVHs) were calculated for a specific set of structures associated with the risk of adverse health outcomes, as listed in Table 4.1. The DVH's are graphs of the dose delivered to a volume of the brain. Specifically, cumulative DVHs show the percentage volume of a structure that received x dose (in Gy) or higher. For example, Figure 4-3 shows that 46.3% of the supratentorial brain received 20 Gy or higher. The data from the DVHs were used to determine the risks of IQ loss and hearing loss. The models from literature used to calculate those health risks are explained in the next section.

Table 4.1: Brain structures related to health outcomes

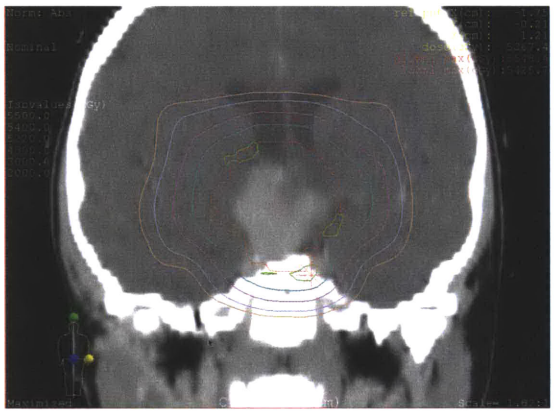
Brain Structure	Health Outcome
Whole brain	Secondary Cancer
Supratentorial brain	IQ Loss
Left Temporal Lobe	IQ Loss
Hypothalamus	GHD, Hypothyroidism
Pituitary Gland	GHD, Hypothyroidism
Cochlea (left and right)	Hearing Loss



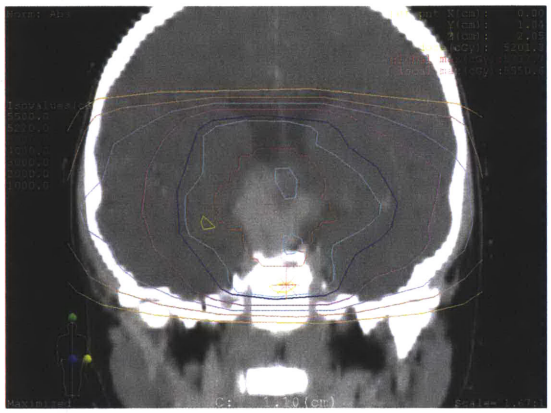
(a) Proton therapy - axial view



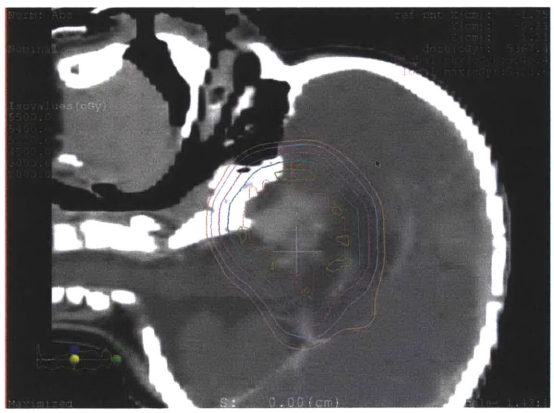
(b) IMRT - axial view



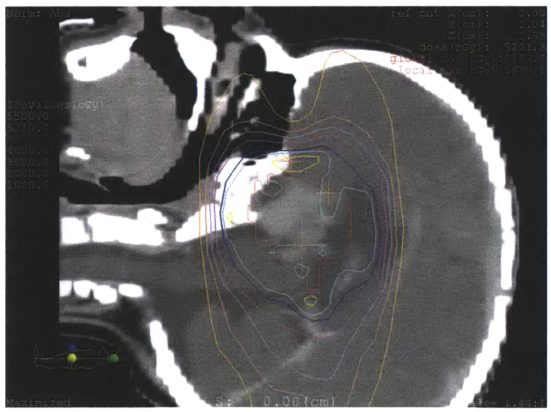
(c) Proton therapy - coronal view



(d) IMRT - coronal view



(e) Proton therapy - sagittal view



(f) IMRT - sagittal view

Figure 4-2: P1 Proton therapy and IMRT treatment plans, as seen from the axial, sagittal, and coronal views. The red contour line delineates the GTV. A comparison of the images show that proton therapy provides an improved dose distribution compared to IMRT by irradiating less brain tissue around the target.

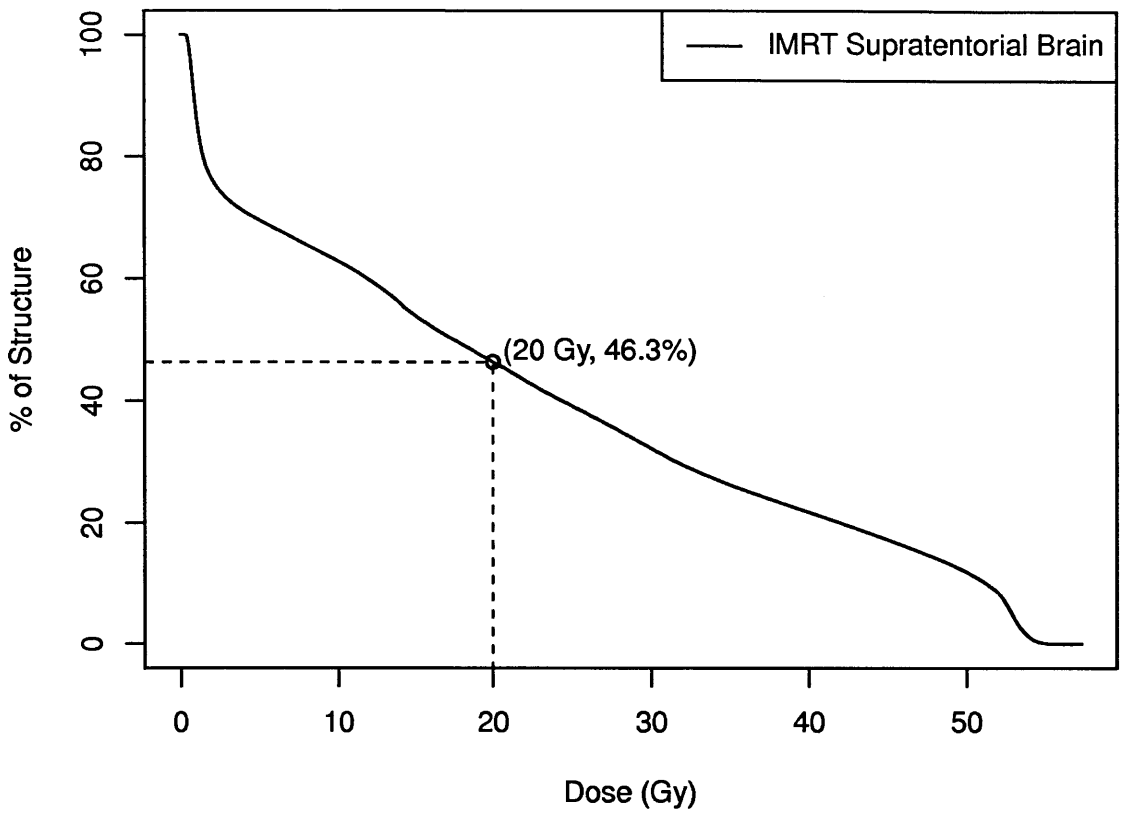


Figure 4-3: Cumulative DVH of supratentorial brain from an IMRT treatment plan. The dashed line helps to indicate the example point that 46.3% of the supratentorial brain received 20 Gy or higher.

4.2 Cost-Effectiveness Model

The cost-effectiveness model in this thesis was designed as a Markov Model using the TreeAge Pro 2009 software. Markov models are decision models designed to account for events that recur over time.[72] Markov models are useful when trying to make decisions about healthcare strategies; in this case, whether to treat LGGs with proton therapy or IMRT.

In a Markov model, a patient is always in one of a set number of health states during each cycle. In that state, the patient experiences various events (for example, getting a secondary cancer) according to the model design. At the end of each cycle, the patient may transition between the health states. A cycle is a length of time during which the patient stays in a particular health state. For a model that evaluates the

lifetime of a population, the cycle time is typically one year. If the patient dies during a given cycle, the patient is sent to the death state. The death state is a terminal state, effectively ending the simulation for that patient.

The model in this thesis was designed to track two hypothetical cohorts of pediatric patients treated for LGGs, one cohort with proton therapy and the other with IMRT. The pediatric patient cohort was evaluated starting at age 5. Each patient's gender was determined at the beginning of the simulation, and the patient was evaluated using the associated gender-specific risks and costs.

The model was designed as a Monte Carlo simulation, where a large number of patients faced with the same health risks are individually tracked. Every cycle, the patient is put in the 'Survive' state where he or she runs the risks of experiencing various adverse health outcomes with their associated costs. The patient goes through the simulation until he/she dies based on the mortality risks detailed below, in which case the patient reaches the terminal 'Death' state.

The Monte Carlo simulations in this model was test with a sample size of 100,000 patients. Each cycle was set to be 1-year. Every cycle, each patient was faced with probabilities of gaining a long-term health effect and dying. Each patient could experience the following health outcomes: IQ loss, GHD, hypothyroidism, hearing loss, and secondary cancer. The patient also ran the risk of death, with the possibility of dying from normal death, tumor recurrence death, or secondary cancer death. Whenever the patient reached the end of a cycle, all their costs incurred that year would be added to the costs from previous years. The patient would run through the model until death, which was forced at age 100 if the patient did not die before then.

4.2.1 Mortality Risks

The model assumed 5 and 10 year survival rates of 98.5% and 95.9%, according to Merchant *et al*'s LGG study. [51] The mortality rate also included a 20-year survival rate of 85% from a follow-up study of 71 pediatric LGG patients between 1956 and 1991. [73] The overall 5-year, 10-year, and 20-year mortality probabilities were 1.5%, 4.1%, and 15% respectively.

Risk of dying from secondary cancer was included from year 1-15 after diagnosis, as shown in Table 4.2. Patients could only incur the risk of secondary cancer death if they had secondary cancer that particular cycle.

Table 4.2: Yearly risk of death due to secondary cancer

Time From Treatment (years)	Probability
1-10	0.13%
11-15	0.12%

The secondary cancer mortality rate was based on the mortality data from the Childhood Cancer Survivor Study. [34] The data are based on the mortality experience of 20,483 U.S. pediatric cancer survivors as of 2002. The CCSS study did not provide risks of death from tumor recurrence for the first four years as the patients were only evaluated starting from 5 years after treatment. In the model, the risk of death due to secondary cancer from years 1-4 after treatment was assumed to be the same as the rate from years 5-10.

Beginning fifteen years after treatment (in the base case, from age 21 on), normal death rates for males and females were applied according to the 2006 U.S. Life Tables. [74]

4.2.2 Risks of Health Outcomes

IQ Loss

The average IQ loss was estimated using the study by Merchant *et al*, which followed a group of 78 LGG pediatric patients treated with radiation therapy (all photon). [42] The study quantified the relationship between radiation dose and IQ score, as shown in Equation 4.1:

$$\text{IQ} = 95.5545 + \text{Age} \times 0.3291 + \text{Time} \times (\text{Age} \times 0.00273 - V_{0-30} \times 0.0027 - V_{30-60} \times 0.0047) \tag{4.1}$$

where *Age* is the age in years when the patient receives radiation treatment, *Time* is the time in months since radiation treatment, V_{0-30} is the percentage of supratentorial brain that received 0 to 30 Gy, and V_{30-60} is the percentage of supratentorial brain that received 30 to 60 Gy.

The number of IQ points lost was determined using Equation 4.1, with the volume inputs taken from the DVHs of the supratentorial brain for proton therapy and IMRT. Merchant *et al*'s analysis did not specify the uncertainty associated with the IQ score calculated form Equation eq:Merch-dose-IQ. However, since Merchant *et al* found that their model could predict IQ score after radiation treatment, the model in this thesis assumed that any difference found in IQ score was significant.

Since the Merchant *et al* study followed the patients' IQ change only up to 5 years after treatment, this model presented here assumed all IQ loss occurs up to 5 years after treatment. The base case assumed that all proton therapy and IMRT patients acquired the full IQ loss calculated using Equation 4.1.

Endocrine Dysfunctions

The model included the risk of GHD and hypothyroidism. For proton therapy, the cumulative 10-year risk of GHD and hypothyroidism were both estimated at 35%, assuming a constant yearly incidence rate of 0.005/person-year. The study by Hug *et al* of 25 pediatric patients treated for LGG using proton therapy found 4 patients (17%) with endocrine complications 3 years after treatment. The follow-up study (n= 116) by Dr. Margaret Pulsifer at MGH found a 21% (n = 24) risk of developing endocrine problems for patients any time between 1 to 10 years post-treatment. The risks of GHD and hypothyroidism in this model were higher than the ones in literature to provide a conservative estimate.

For IMRT, the 10-year GHD and hypothyroidism risks were estimated at 49% and 68%, respectively, based on Merchant *et al*'s study. [51] The model assumed that the rate of GHD and hypothyroidism incidence were constant over the 10 years post-treatment (0.006/person-year and 0.01/person-year).

After year 10 (after treatment), the risk of GHD and hypothyroidism were reduced

to 0%. This assumption was made in the model as not enough reliable data was available beyond the 10-year follow-up. Furthermore, the model assumed that ten years after treatment, patients would be 15 years old and would no longer need to receive growth hormones since growth hormone therapy usually ends for children during their mid to late teenage years. [58]

Growth hormone therapy was terminated after age 16 for males and age 14 for females, as the accepted ages when children reach their final height. [58] Studies have shown that a certain number of the patients who received growth hormone therapy as children are still growth hormone deficient when they reach adulthood. [51] [57] However, those patients do not often receive growth hormone treatment even though they might need it as they are not tested for GHD at their final height.

Hearing Loss

The risk of hearing loss was based on a study by Chiaho Hua *et al* relating hearing loss to the cochlea dose given to pediatric patients treated for brain tumors. [44] The risk of hearing loss varied according to mean dose delivered to cochlea, as shown in Table 4.3.

Table 4.3: Risk of hearing loss based on average dose to cochlea

Dmean	Risk
less than 35	0%
35-44	0-16%
45-54	0-20%
55 and higher	17-49%

All cases of hearing loss were assumed to occur on year 3 after treatment, based on the Hua *et al* study that found most hearing loss onset at year 3.3. The model used a uniform risk based on Table 4.3 of acquiring a hearing loss on either ear.

Secondary Cancer

The risk of secondary cancer was based on the study by Winkfield ??, which modeled the risk of secondary cancer for proton therapy and IMRT. [67] In this model, the yearly probability of secondary cancer was 0.12% for proton therapy and 0.18% for IMRT. The probability of getting secondary cancer at each cycle is defined in Table 4.4. The probabilities of secondary cancer were based on Winkfield *et al*'s results for 3-field treatments.

The risk of getting a secondary cancer was set to zero at 15 years after treatment. Follow-up data of patients beyond 15 years after treatment are difficult to obtain, and the current clinically studies published on the risk of secondary cancer generally only provide confident estimates up to 10 years after treatment. [66] [68] In this model, each patient could only get secondary cancer once in their lifetime.

Table 4.4: Yearly sisk of secondary cancer for proton therapy and IMRT

Time Since Treatment (Years)	Proton	IMRT
1-15	0.12%	0.18%
16+	0%	0%

4.2.3 Costs Estimation

Proton and IMRT Treatment

The cost of proton therapy was estimated at $58,000/treatment. A recent study by Peeters et al found that the treatment of head and neck tumors was €39,610, or $58,971 in 2011 dollars, for proton therapy. [75] The cost-effectiveness analysis of proton therapy for prostate cancer also estimated the cost at $58,000/treatment. [70]

Proton beam therapy is generally accepted at being twice as expensive as IMRT. A cost study by by Goitein and Jermann estimated the proton therapy/IMRT cost ratio at 2.1. [12] The model used the 2.1 cost ratio as the base case, estimating the

cost of IMRT at $24,000/treatment. Peeters et al found a ratio of 3.2 for the cost ratio, and this value was used in the sensitivity analysis. [75]

IQ Loss

The cost of IQ loss is associated with income loss. The yearly income loss was set at 1.931%/IQ point for men and 3.225%/IQ point for women. The average income used was $45,485/year for men and $35,549/year for women, according to the U.S. Census Bureau Report for 2009. [76] Income loss occured from age 18 to 65. The rates of income loss due to IQ loss were based on a study by Salkaver that reviewed the expected earning loss from children affected by lead poisoning. [77] Those children were likely to have a lower IQ depending on the lead dose, which in turn negatively impacted their education and earning potential.

The general threshold for an individual to be considered intellectually disabled is an IQ score of 70 or lower. [78] In this model, the cost of IQ loss also included the cost of special education from age 4 to 18 if the patients' IQ score was 70 or below. The cost of special education was estimated at $15,000/child-year. The U.S. Department of Education evaluated a cost of $12,474/child-year in in their 2002 report, which is roughly equivalent to $15,000 in 2011 dollars.[79]

Endocrine Dysfunctions

The cost associated with GHD varies between $5,000-$27,000/year, based on the cost of Omnitrope and Tev Tropin ($30/mg). [80] The GH dose prescribed is 0.3 mg/kg-week, based on the patient's weight. [81] Using weight charts for American males and females, the prescribed dose and cost was determined for each age, as shown in Table 4.5. [82]

Males receive a dose of 0.3 mg/kg-week up to age 16. Females receive a dose of 0.3 mg/kg-week up to age 14. After that age, the dose drops to 10% of the original prescription or 0.03 mg/kg-week. The base case assumed that patients stopped taking growth hormones at age 16 for males and age 14 for females, which is when they typically stop growing.??

Table 4.5: Yearly GHD costs by age based on the 50th percentile weight of the U.S. population

	Male			Female		
Age (years)	Weight (kg)	Dose (mg/week)	Cost ($/year)	Weight (kg)	Dose (mg/week)	Cost ($/year)
2	13.4	4.0	5,803	12.8	3.8	5,539
3	15.3	4.6	6,590	14.7	4.4	6,329
4	17.3	5.2	7,472	16.7	5.0	7,201
5	19.5	5.9	8,437	18.9	5.7	8,155
6	21.9	6.6	9,445	21.3	6.4	9,186
7	24.3	7.3	10,511	23.9	7.2	10,333
8	27.1	8.1	11,690	27.0	8.1	11,658
9	30.2	9.1	13,046	30.6	9.2	13,208
10	33.9	10.2	14,629	34.7	10.4	14,975
11	38.1	11.4	16,472	39.1	11.7	16,874
12	43.0	12.9	18,573	43.4	13.0	18,758
13	48.3	14.5	20,860	47.4	14.2	20,459
14	53.7	16.1	23,188	50.6	15.2	21,837
15	58.7	17.6	25,347	-	-	-
16	62.8	18.9	27,145	-	-	-

The cost of hypothyroidism was $168/year, based on the cost of the generic drug Levothyroxine Sodium at $14/month for a dose of 75 mcg/day.?? The cost of the generic drug was used to assume the least costly scenario. Patients needing thyroid hormone replacement had a yearly recurring cost until death.

Patients with endocrine complications saw an endocrinologist on average 3 times per year. [58] The model included physician costs for patients with either GHD or hypothyroidism (Table 4.6). The physician costs were derived from interviews requesting consultation quotes from MGH and the Mayo Clinic. [58] [83]

Hearing Loss

The cost of a hearing aid was estimated at $2,500/ear, with the cost recurring every 5 years. [84] An additional audiologist visit cost of $750 also recurred every 5 years. The values were based on an interview requesting consultation quotes from

Table 4.6: Costs of visits to endocrinologist

		Cost/Visit	# of Visits	Total
Year 1	Consultation	$816	1	
Year 1	Follow-Up	$280	2	$1376
All other years	Follow-Up	$280	3	$840

the Massachusetts Eye and Ear Hospital. [85]

Secondary Cancer

The cost of secondary cancer was $24,143/case based on the average cost of pediatric secondary cancer cases in the U.S. (cost was updated from $21,100 in 2005 to 2011 currency). [86] [87]

4.3 Sensitivity Analysis

To test the robustness of the results, certain parameters in the model were changed. The sensitivity analysis varied three aspects of the model: 1) mortality rates based on tumor recurrence data from the Childhood Cancer Survivor Study, 2) costs of radiation treatment, and 3) costs of GHD treatment based on higher average weight estimates. The sensitivity analysis was applied to the models using P1 and P2 input data holding everything constant except for the specific change of interest. Only one parameter was varied at a time.

Tumor Recurrence Rate

The mortality risk was changed to include mortality data from the Childhood Cancer Survivor Study. [34] The data is based on the mortality experience of 20,483 U.S. pediatric cancer survivors as of 2002. The risk of death due to tumor recurrence for all cancer patients were used from year 5-34 after diagnosis, as shown in Table 4.7.

The yearly risk of death estimated in Table 4.7 included both the risk of tumor

Table 4.7: Yearly risk of death due to tumor recurrence

Time From Treatment (years)	Risk
5-10	1.02%
11-14	0.46%
15-19	0.35%
20-24	0.35%
25-29	0.44%
30-34	0.68%

recurrence and 'other' death from the Armstrong *et al* study. [34] The risk of 'other' death included any patients who died from reasons that were not due to secondary cancer, tumor recurrence, cardiac,pulmonary, and external causes. The CCSS study did not provide risks of death from tumor recurrence for the first four years as the patients were only evaluated starting from 5 years after treatment. From year 1-4 after treatment, this model assumed that the risk of death due to tumor recurrence were the same as in the base case.

Five years after treatment (from age 16 on), normal death rates for males and females were also applied according to the 2006 US Life Tables. [74] The normal death rates were used to account for any death unrelated to the tumor.

Cost of Radiation Treatment

A study by Goitein and Jermann determined the cost of treatment per fraction to be €1025 for protons and €425 for IMRT (in 2003 currency). [12] Assuming an average conversion rate of \$1 to €1.07 in 2003, the cost per fraction is \$1160 for proton therapy and \$481 for IMRT (in 2011 dollars). [88] [87] For a 30-fraction LGG treatment, the cost of proton therapy and IMRT was estimated at \$35,000 and \$15,000 respectively in the sensitivity analysis. Another analysis tested the 3.2 proton therapy/IMRT cost ratio estimated by Peeters *et al.*, with cost of treatment estimated at \$58,000 for proton therapy and \$18,000 for IMRT.

Higher GHD Costs

Studies have shown that there is an increased chance of obesity in pediatric population treated with radiation therapy. [89] [90] The Childhood Cancer Survivor Study that leukemia survivors treated with 20 Gy CRT were more likely to be obese than the general population (2.72 times higher for females, 1.66 times higher for males). [91] The patients weight was increased to match the average of children in the 75thpercentile weight of the US population. The costs of growth hormone therapy were updated to match the higher weights, as shown in Table 4.8.

Table 4.8: Yearly GHD costs by age based on the 75th percentile weight of the U.S. population

	Male			Female		
Age (years)	Weight (kg)	Dose (mg/week)	Cost ($/year)	Weight (kg)	Dose (mg/week)	Cost ($/year)
2	14.5	4.3	6254	13.9	4.2	5989
3	16.5	5	7141	16.0	4.8	6911
4	18.9	5.7	8156	18.4	5.5	7935
5	21.5	6.4	9279	21.0	6.3	9051
6	24.2	7.3	10462	23.8	7.1	10266
7	27.1	8.1	11726	26.9	8.1	11639
8	30.4	9.1	13145	30.7	9.2	13248
9	34.3	10.3	14796	35.0	10.5	15134
10	38.7	11.6	16725	40.0	12	17259
11	43.8	13.1	18934	45.1	13.5	19498
12	49.5	14.8	21370	50.1	15	21659
13	55.4	16.6	23926	54.5	16.3	23539
14	61.2	18.4	26441	57.9	17.4	24992
15	66.5	19.9	28723	-	-	-
16	70.9	21.3	30611	-	-	-

This chapter describes the methods used in this study to compare proton therapy and IMRT. The following chapter provides the long-term health effect and cost results from the model simulations based on P1 and P2's treatment plans. The results from the sensitivity analysis and IQ analysis of patients P3 and P4 are also presented.

Chapter 5

Results

In this chapter, the results of the Markov model described in Chapter 4 are presented, and conclusions based on the expected long-term health effects and costs incurred from proton therapy and IMRT are discussed. The first two sections present the results of the model simulations based on P1 and P2 treatment plans, comparing the health effects and costs associated with the two treatment modalities. The final section further explores the relative difference in total IQ loss between the two modalities using treatment plans from patients P3 and P4.

All costs are presented to the nearest thousands of dollars as the cost results are not significant to the hundreds of dollars or lower. The rounding of the results does not influence the conclusions of this thesis.

5.1 Results using P1's Proton Therapy and IMRT Treatment Plans

The modeled change in IQ score for P1 was considerable for both proton therapy and IMRT (Figure 5-1). From a starting point of IQ = 97, the IQ score drops to 80 points for proton therapy and 78 points for IMRT. The relative difference in total IQ loss between modalities was small, with IMRT overall incurring an additional 2-point loss compared to proton therapy (Table 5.1).

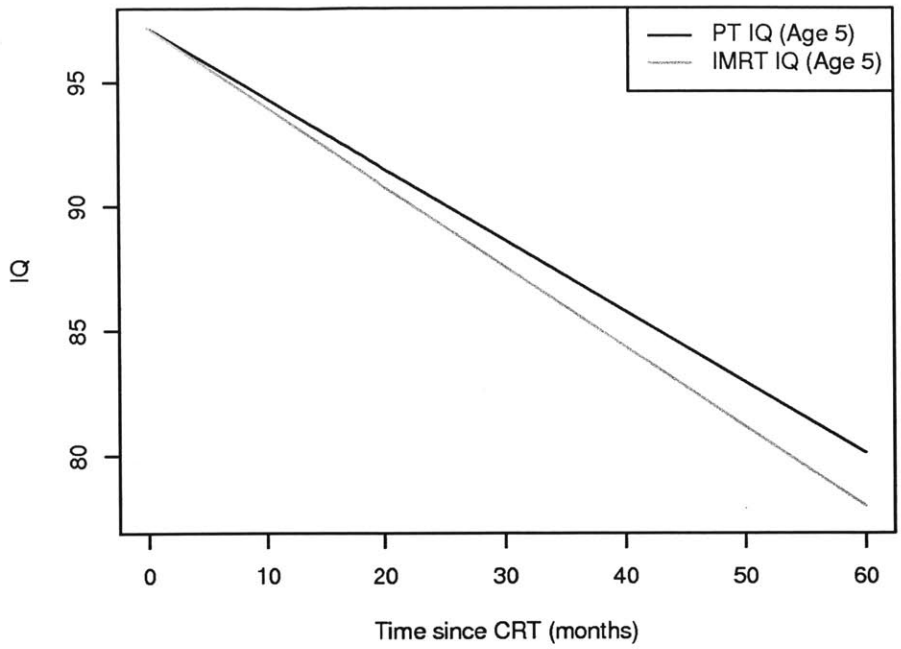


Figure 5-1: Expected IQ score as a function of time for P1 after receiving radiation treatment at age 5.

Table 5.1: P1 Estimated IQ points loss after receiving radiation treatment at age 5

Time since CRT	IQ Loss (pts)	
(months)	Proton Therapy	IMRT
12	3	4
24	7	8
36	10	12
48	14	15
60	17	19

Table 5.2 shows the V_{0-30} and V_{30-60} split for supratentorial brain. Proton therapy delivers a high dose (30-60 Gy) to a lesser volume of the supratentorial brain than IMRT. Based on P1's cochlea DVH data, the risk of hearing loss was 0% for both proton therapy and IMRT (Table 5.3).

The model found that proton therapy always resulted in a lower risk of acquiring a long-term health effect for GHD, hypothyroidism, and secondary cancer, as shown in Table 5.4. There was no difference in risk of hearing loss (Table 5.3). In the

Table 5.2: Volume of supratentorial brain that received 0-30 Gy and 30-60 Gy based on P1's treatment plans

	V_{0-30}	V_{30-60}
Proton Therapy	85%	15%
IMRT	67%	33%

Table 5.3: P1 risk of hearing loss

		Mean Dose (Gy)	Risk
Proton Therapy	Right Cochlea	3	0%
	Left Cochlea	2	0%
IMRT	Right Cochlea	21	0%
	Left Cochlea	15	0%

simulation, the model assigned IQ loss estimated for P1 to all patients.

Table 5.4: P1 Modeled risks of long-term health effects

	IQ Loss	GHD	Hypothyroidism	Hearing Loss	Secondary Cancer
Proton Therapy	100%	32%	32%	0%	2%
IMRT	100%	43%	56%	0%	3%
Difference	0%	-10%	-23%	0%	-1%

The model found a large lifetime cost associated with long-term health effects: an average of $349,000/patient for proton therapy and $365,000/patient for IMRT (Table 5.5). IMRT was found to be more expensive with an average cost difference of $17,000/patient (Table 5.5). The majority of the total cost was due to IQ loss ($246,000/patient for proton therapy and $275,000/patient for IMRT), reflecting that a small change in IQ points could lead to a significant long-term cost difference. If IQ loss is not considered in the cost comparison, proton therapy was found to be more expensive than IMRT by $12,000/patient.

Table 5.5: P1 Total cost comparison between proton therapy and IMRT

	Proton Therapy ($)	IMRT ($)	Difference ($)*
Treatment Cost	58,000	28,000	30,000
IQ Loss	246,000	275,000	-29,000
Endocrine Dysfunction	44,000	62,000	-18,000
Hearing Loss	0	0	0
Secondary cancer	400	500	-200
Total	349,000	365,000	-17,000
Total without IQ	102,000	90,000	12,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

Endocrine dysfunction was the second largest driver of cost ($32,000/patient for proton therapy and $44,000/patient for IMRT), with GHD contributing the largest proportion of that cost (Table 5.6).

Table 5.6: P1 Detailed endocrine dysfunction cost comparison between proton therapy and IMRT

	Proton Therapy ($)	IMRT ($)	Difference ($)*
GHD	32,000	44,000	-12,000
Hypothyroidism	1,000	2,000	-1,000
Endocrinologist Visit	11,000	16,000	-5,000
Total	44,000	62,000	-18,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

For proton therapy, the breakdown of total costs shows that the majority of the total costs incurred by each patient fall in the $240,000-480,000 range (Figure 5-2). That range of high costs in Figure 5-2 reflect the costs accumulated from IQ loss for the patients who did not experience death due to tumor recurrence or secondary cancer. That population represents 85% of the total sample population, as shown in Table 5.7. Those patients lived to be on average 70 years old and incurred the full cost of IQ loss from age 18-65. With a 17 points IQ loss, the maximum lifetime cost associated with IQ loss is $219,482 for males and $286,487 for females. The maximum lifetime GHD cost is $159,632 for males and $139,367 for females. The low total costs

(below $240,000) reflect the population that dies early. Costs savings occur when the population dies early as an artifact of the model, which will be discussed in Chapter 6.

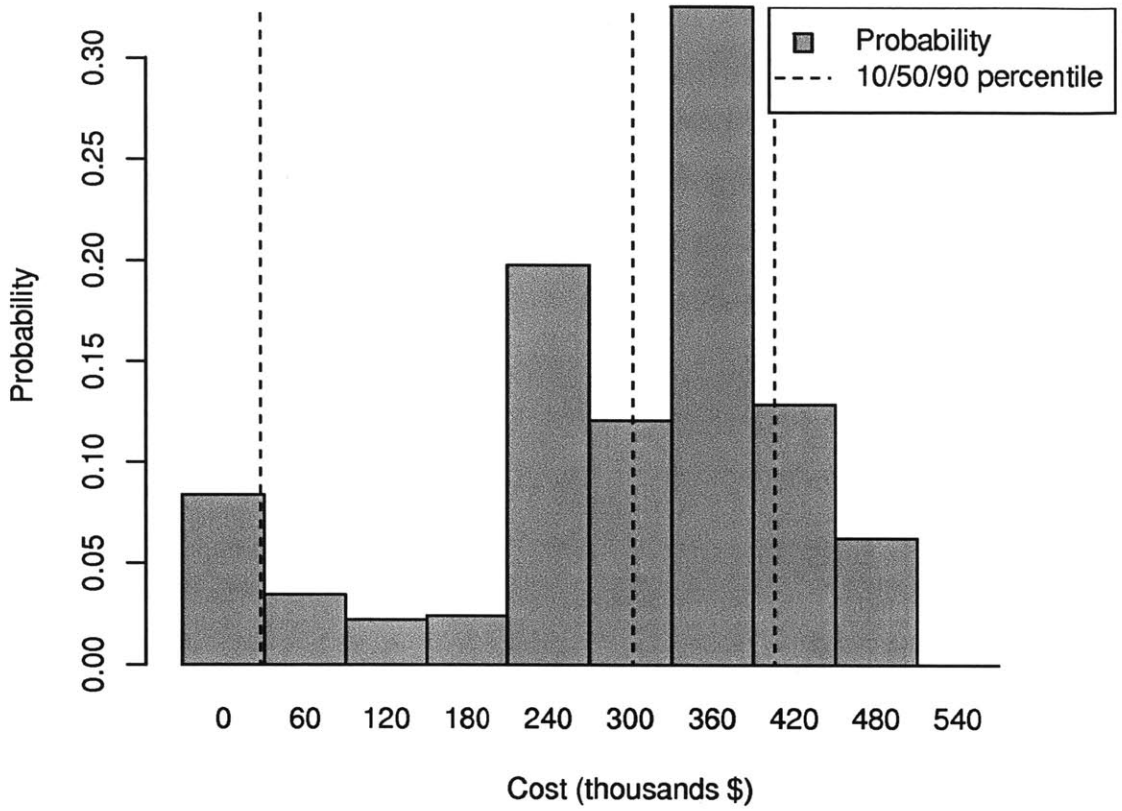


Figure 5-2: P1 Probability of total cost per patient due to long-term health effects from proton therapy.

Table 5.7: P1 Risk of normal death, tumor recurrence death,and secondary cancer

	Normal Death	Tumor Recurrence	Secondary Cancer
Proton	85.6%	14.3%	0.1%
IMRT	84.3%	14.2%	0.1%

The risk of secondary cancer death was low because patients could only face that risk once they acquired a secondary cancer. However, the results show that there is only a small chance of secondary cancer in a patient's lifetime (2% for proton therapy

and 3% for IMRT). Consequently, the risk of death due to secondary cancer is very low (0.1% for both treatment modalities).

For IMRT, the individual breakdown of total costs shows that the majority of the total costs incurred by each patient fall in the \$300,000-480,000 range (Figure 5-3). That cluster of high costs (greater than \$300,000) reflects the population that live beyond the risk of death due to tumor recurrence and secondary cancer. The population who survive past age 25 face normal death rates and survive until an average age of 70. With a 19-point IQ loss, the maximum lifetime IQ cost is \$245,303 for males and \$320,191 for females.

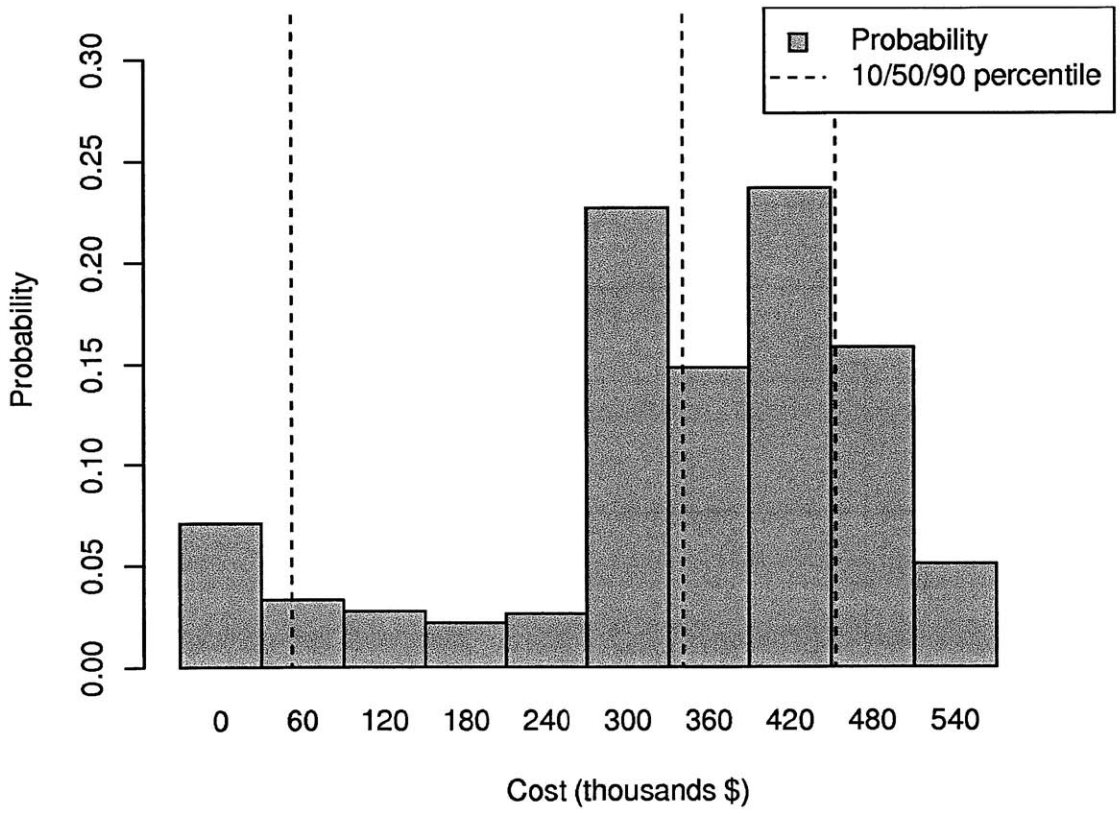


Figure 5-3: P1 Probability of lifetime cost per patient due to long-term health effects from IMRT treatment

5.2 Results using P2's Proton Therapy and IMRT Treatment Plans

The expected change in IQ score for P2 is high for both proton therapy and IMRT (Figure 5-4). From a starting score of IQ = 97, the IQ score dropped to 82 points for proton therapy and 81 points for IMRT. The relative difference in total IQ loss between modalities is small however, with IMRT overall incurring an additional 1-point loss compared to proton therapy (Table 5.8).

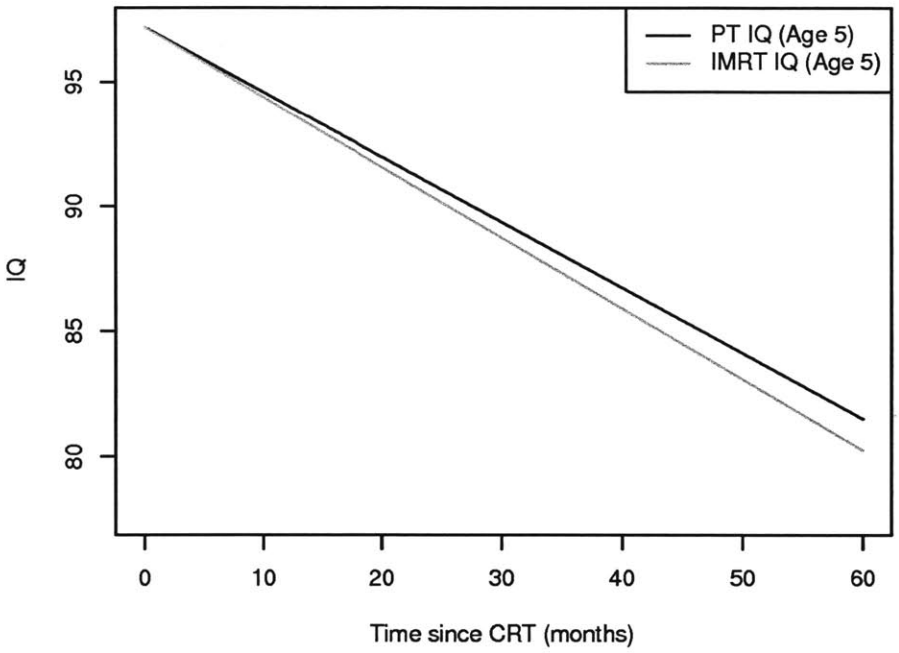


Figure 5-4: Expected IQ score as a function of time for P2 after receiving radiation treatment at age 5

Table 5.9 shows the V_{0-30} and V_{30-60} split for the supratentorial brain. Proton therapy delivers a higher dose (30-60 Gy) to a lesser volume of the supratentorial brain than IMRT. Based on P2's cochlea DVH data, the risk of hearing loss was 0% for proton therapy and 0-16% for IMRT (Table 5.10), according to the study by Hua *et al.* [44] The model found that proton therapy always resulted in a lower incidence of long-term health effects for GHD, hypothyroidism, secondary cancer, and hearing loss as shown in Table 5.11.

Table 5.8: P2 Estimated IQ points loss after receiving radiation treatment at age 5

Time since CRT (months)	Proton Therapy (pts)	IMRT (pts)
12	3	3
24	6	7
36	9	10
48	13	14
60	16	17

Table 5.9: Volume of supratentorial brain that received 0-30 Gy and 30-60 Gy based on P2's treatment plans

	V_{0-30}	V_{30-60}
Proton Therapy	97%	3%
IMRT	87%	13%

Table 5.10: P2 Risk of hearing loss

		Mean Dose (Gy)	Risk
Proton Therapy	Right Cochlea	2	0%
	Left Cochlea	7	0%
IMRT	Right Cochlea	35	0-16%
	Left Cochlea	35	0-16%

Table 5.11: P2 Modeled risks of long-term health effects

	IQ Loss	GHD	Hypothyroidism	Hearing Loss	Secondary Cancer
Proton Therapy	100%	32%	32%	0%	2%
IMRT	100%	43%	56%	8%	3%
Difference	0%	-10%	-23%	-8%	-1%

For P2, the model found an average cost associated with long-term health effects of $334,000/patient for proton therapy and $343,000/patient for IMRT (Table 5.12).

IMRT was more costly, with an average cost difference of $9,000/patient (Table 5.12). The majority of the total cost was due to IQ loss ($232,000/patient for proton therapy and $246,000/patient for IMRT). The overall cost from IQ loss was lower than observed in the P1 simulation since P2's treatment plans resulted in a higher estimated IQ score for both proton therapy and IMRT. Furthermore, the difference in IQ loss cost between proton therapy and IMRT for P1 and P2 ($29,000/patient for P1 and $14,000/patient for P2) reflects the difference in costs expected from a change of 1 IQ point - i.e roughly $14,000/patient per IQ point. If IQ loss is not considered in the P2 cost comparison, proton therapy was found to be more expensive than IMRT by $5,000/patient. The total difference without consideration of IQ loss was lower for P2 than for P1 because the P2 IMRT patients incurred an extra cost from hearing loss. Endocrine dysfunction was the second largest driver of cost ($44,000/patient for proton therapy and $62,000 for IMRT), with GHD contributing to the largest proportion of that cost (Table 5.13). The risks of death were the same for the P1 and P2 simulations (Table 5.14).

Table 5.12: P2 Total cost comparison between Proton Therapy and IMRT

	Proton Therapy ($)	IMRT ($)	Difference ($)*
Treatment Cost	58,000	28,000	30,000
IQ Loss	232,000	246,000	-14,000
Endocrine Dysfunction	44,000	62,000	-18,000
Hearing Loss	0	7,000	-7,000
Secondary cancer	400	500	-200
Total	334,000	343,000	-9,000
Total without IQ	102,000	97,000	5,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

For proton therapy, the breakdown of total lifetime costs shows that the majority of the total costs incurred by each patient fall in the $240,000-420,000 range (Figure 5-5). The maximum lifetime IQ loss costs from a 16-point drop is $206,571 for males and $269,635 for females. The individual breakdown of total costs shows that 75% of the total costs incurred by each patient fall in the $240,000-480,000 range for IMRT

Table 5.13: P2 Detailed endocrine dysfunction cost comparison between proton therapy and IMRT

	Proton Therapy ($)	IMRT ($)	Difference ($)*
GHD	31,000	43,000	-12,000
Hypothyroidism	1,000	2,000	-1,000
Endocrinologist Visit	11,000	16,000	-5,000
Total	44,000	62,000	-18,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

(Figure 5-6). The cluster of high costs (greater than $300,000) reflects the population that pass the risk of death due to tumor recurrence and secondary cancer.

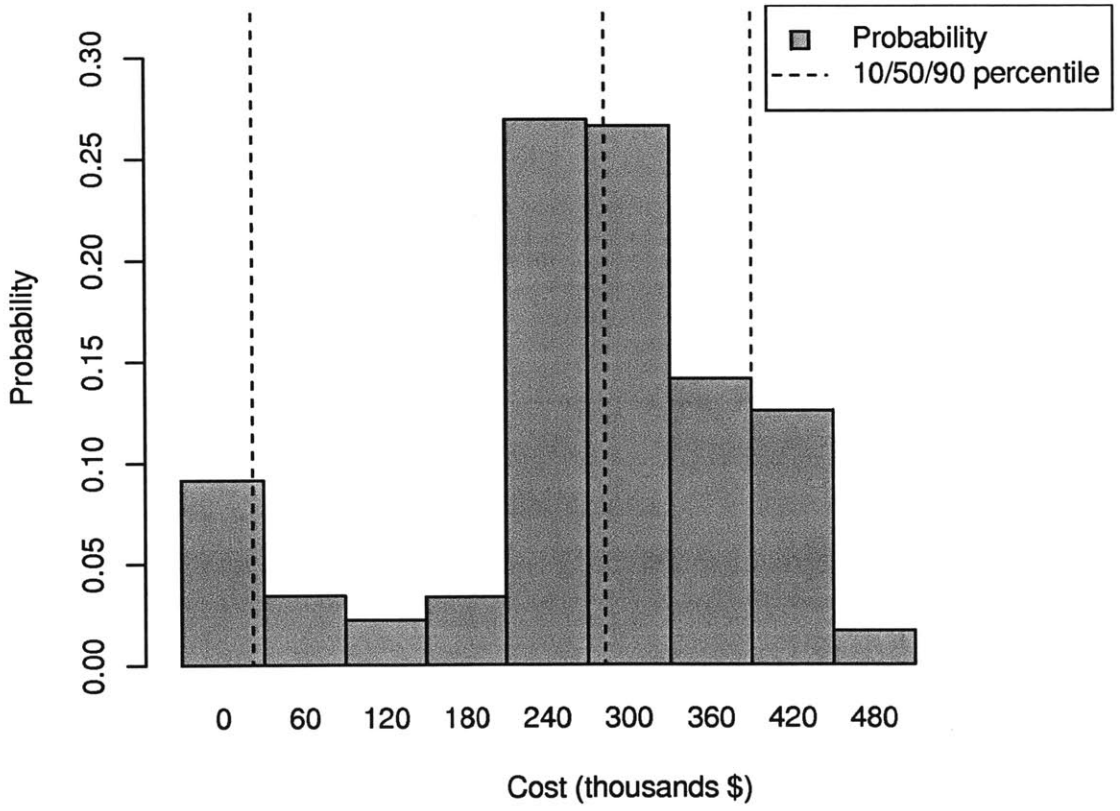


Figure 5-5: P2 Probability of lifetime cost per patient due to long-term health effects from proton therapy.

The results based on P1 and P2's treatment plans show that proton therapy is the dominant treatment modality. Proton therapy results in lower incidences of long-term

Table 5.14: P2 Risk of normal death, tumor recurrence death,and secondary cancer

	Normal Death	Tumor Complications	Secondary Cancer
Proton Therapy	85.6%	14.3%	0.1%
IMRT	85.5%	14.3%	0.1%

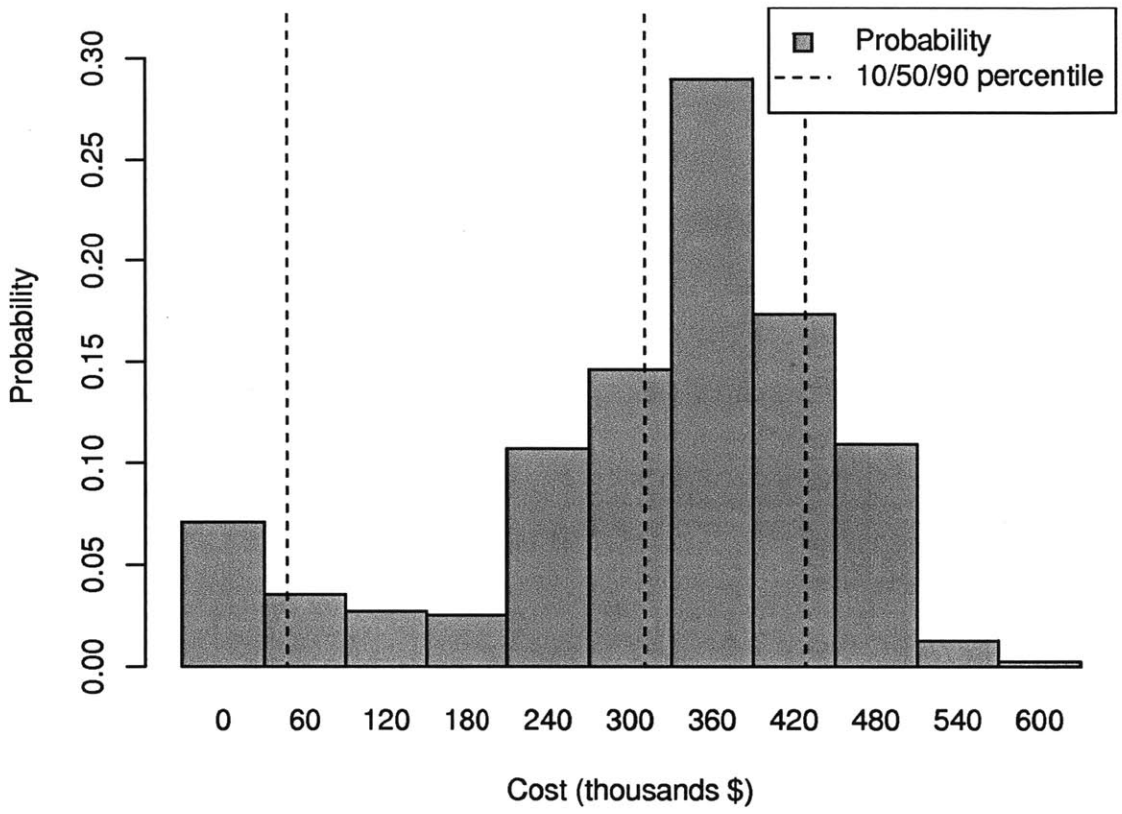


Figure 5-6: P2 Probability of lifetime cost per patient due to long-term health effects from IMRT

health effects and expected overall lower costs than IMRT, by $17,000/patient based on P1's estimated health risks and $9,000/patient based on P2's estimated health risks. The cost associated with IQ loss was the main driver of total costs. However, the relative difference in IQ between proton therapy and IMRT was small for both patients (a 2-point difference in IQ score for P1 and a 1-point difference in IQ score for P2).

5.3 Sensitivity Analysis

The sensitivity analysis varied particular aspects of the model, namely:

1. Mortality rates based on tumor recurrence data from the Childhood Cancer Survivor Study.

2. Costs of radiation treatment.

3. Costs of GHD treatment based on higher average weight estimates.

The sensitivity analysis was applied to the models using P1 and P2 health risks, holding everything constant except for the specific change of interest. Only one parameter was varied at a time.

5.3.1 Tumor Recurrence Rate

The initial analysis assumed mortality rates due to tumor recurrence or tumor related complications for up to 20 years after treatment. The first variation on the base case applied higher mortality rates due to tumor recurrence based on the Childhood Cancer Survivor Study for up to 34 years after treatment. Patients lived on average until age 60 for the CCSS tumor rate case and age 70 for the base case. Patients in the higher mortality rates case were subjected to fewer long-term costs since they had died and the cost of reduced IQ was no longer accrued. The average lifetime cost per patient was $325,000 for proton therapy and $338,000 for IMRT for the case of higher tumor recurrence rate using the P1 simulation (Table 5.15). The cost savings were not as high in the sensitivity analysis as fewer patients experienced the higher range of IQ loss cost. In the base case, since the patients lived longer, they were subjected to higher IQ loss costs.

The average lifetime cost per patient was $312,000 for proton therapy and $320,000 for IMRT for the case of higher tumor recurrence rate using the P2 simulation(Table 5.16). The cost savings were not very different between the higher tumor recurrence case and base case: $7,000/patient compared to $9,000/patient in the base case.

Table 5.15: P1 Comparison of total costs between base case and case with higher probability of death due to tumor recurrence

	High Recurrence Rate			Base Case		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
Treatment Cost	58,000	28,000	30,000	58,000	28,000	30,000
IQ Loss	224,000	250,000	-26,000	246,000	275,000	-29,000
Endocrine Dysfunction	43,000	61,000	-17,000	44,000	62,000	-18,000
Hearing Loss	0	0	0	0	0	0
Secondary cancer	400	500	-200	400	500	-200
Total	325,000	338,000	-13,000	349,000	365,000	-17,000
Total without IQ	102,000	89,000	13,000	102,000	90,000	12,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

Table 5.16: P2 Comparison of total costs between base case and case with higher probability of death due to tumor recurrence

	High Recurrence Rate			Base Case		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
Treatment Cost	58,000	28,000	30,000	58,000	28,000	30,000
IQ Loss	211,000	224,000	-13,000	232,000	246,000	-14,000
Endocrine Dysfunction	43,000	61,000	-17,000	44,000	62,000	-18,000
Hearing Loss	0	7,000	-7,000	0	7,000	-7,000
Secondary cancer	400	500	-200	400	500	-200
Total	312,000	320,000	-7,000	334,000	343,000	-9,000
Total without IQ	102,000	96,000	6,000	102,000	97,000	5,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

5.3.2 Cost of Radiation Treatment

The second variation looked at a lower cost of radiation therapy treatment. In the base case, the cost treatment was $58,000/patient for proton therapy and $28,000/patient for IMRT. In this variation, the cost of proton therapy was $35,000/patient and the cost of IMRT was $15,000/patient. The difference between the two treatments was also lowered: $20,000 as compared to $30,000 in the base case. The lower treatment

cost difference resulted in higher cost savings for the P1 and P2 cases. However, if the cost of IQ loss was not accounted for, only the P2 case resulted in cost savings for proton therapy (Table 5.17). That is, when IQ loss is not considered, proton therapy is more expensive by ~$5,000.

Table 5.17: Difference in total costs for case with treatment priced at $35,000/patient for proton therapy and $15,000/patient for IMRT

	P1			P2		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
Treatment Cost	35,000	15,000	20,000	35,000	15,000	20,000
IQ Loss	246,000	275,000	-29,000	232,000	246,000	-14,000
Endocrine Dysfunction	44,000	62,000	-18,000	44,000	62,000	-18,000
Hearing Loss	0	0	0	0	7,000	-7,000
Secondary cancer	400	500	-200	400	500	-200
Total	326,000	353,000	-27,000	311,000	330,000	-19,000
Total without IQ	79,000	78,000	2,000	79,000	84,000	-5,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

Another case variation analyzed the effect of a higher treatment ratio between proton therapy and IMRT. Using Peteers *et al*'s proton therapy to IMRT cost ratio of 3.2 ($58,000 for proton therapy and $18,000 for IMRT), the model found that proton therapy was not cost effective for the P2 case as the average total costs were slighty higher for proton therapy by $1,000.

5.3.3 Cost of GHD

The final sensitivity analysis used a higher average weight to calculate the cost of GHD. Since the cost of GHD is proportional to the weight of the patient, a higher average weight resulted in a higher cost of GHD. The higher cost of GHD was reflected in the higher average total cost per patient: $430,000 for proton therapy and $473,000 for IMRT in the P1 case, $416,000 for proton therapy and $451,000 for IMRT in the P2 case (Table 5.19). This higher cost associated with GHD resulted in a higher cost savings for proton therapy. With the higher GHD costs, proton therapy is always more

Table 5.18: Difference in total costs for case with proton therapy and IMRT treatment cost ratio of 3.2

	P1			P2		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
Treatment Cost	58,000	18,000	40,000	58,000	18,000	40,000
IQ Loss	246,000	275,000	-29,000	232,000	246,000	-14,000
Endocrine Dysfunction	44,000	62,000	-18,000	44,000	62,000	-18,000
Hearing Loss	0	0	0	0	7,000	-7,000
Secondary cancer	400	500	-200	400	500	-200
Total	349,000	356,000	-7,000	334,000	334,000	1,000
Total without IQ	102,000	81,000	22,000	102,000	88,000	15,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

cost effective than IMRT, even in the case where IQ loss is not considered. GHD cost is the main driver of endocrine dysfunctions cost in the case where patients with a higher average weight are considered (Table 5.20).

Table 5.19: P1 and P2 Difference in total costs based on the 75th percentile weight of the U.S. population

	P1			P2		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
Treatment Cost	58,000	28,000	30,000	58,000	28,000	30,000
IQ Loss	246,000	275,000	-29,000	232,000	247,000	-15,000
Endocrine Dysfunction	126,000	170,000	-44,000	126,000	169,000	-43,000
Hearing Loss	0	0	0	0	7,000	-7,000
Secondary cancer	400	500	-200	400	500	-200
Total	430,000	473,000	-43,000	416,000	451,000	-35,000
Total without IQ	184,000	198,000	-14,000	184,000	205,000	-20,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

Table 5.20: P1 and P2 Difference in total endocrine dysfunction costs by age based on the 75th percentile weight of the U.S. population

	P1			P2		
	PT ($)	IMRT ($)	Diff.* ($)	PT ($)	IMRT ($)	Diff.* ($)
GHD	113,000	151,000	-38,000	113,000	151,000	-38,000
Hypothyroidism	1,000	2,000	-1,000	1,000	2,000	-1,000
Endocrinologist Visit	11,000	16,000	-5,000	11,000	16,000	-5,000
Total	126,000	170,000	-44,000	126,000	169,000	-43,000

* Difference is equal to the cost of proton therapy minus the cost of IMRT

5.4 IQ Analysis on P3 and P4

The DVHs for P3 and P4 showed that there was not a large difference in the volume of the supratentorial brain that received 30 Gy or higher between proton therapy and IMRT (Table 5.21). That similarity between the two plans resulted in almost the same change in IQ score (Table 5.22).

Table 5.21: Volume of supratentorial brain that received 0-30 Gy and 30-60 Gy for P3 and P4's treatment plans

	P3		P4	
	Proton Therapy	IMRT	Proton Therapy	IMRT
V_{0-30}	98%	91%	78%	65%
V_{30-60}	2%	9%	22%	35%

The results of the simulations showed that proton therapy decreases the risk of long-term health effects and costs incurred in the case of the two patients analyzed in this thesis. Costs associated with IQ loss were the main drivers of total costs. However, the difference in IQ loss between the two modalities was not large (on the order of 1 or 2 IQ points difference). Chapter 6 will discuss the results described in this chapter, providing explanations for the differences in the long-term health effects and costs between proton therapy and IMRT.

Table 5.22: IQ score change based on P3 and P4's treatment plans

	P3		P4	
Time since CRT (months)	Proton Therapy	IMRT	Proton Therapy	IMRT
0	97	97	97	97
12	94	94	94	93
24	91	91	90	89
36	88	87	86	85
48	85	84	83	82
60	82	81	79	78

Chapter 6

Discussion

In the previous chapter, proton therapy was found to reduce the incidence of long-term health effects and their associated costs when compared to IMRT. Proton therapy was more cost-effective than IMRT, except for the case when the cost from IQ loss was not included or when the cost difference between the two treatment plans was increased. This chapter provides a discussion of the long-term health and costs results, explaining why the differences presented in Chapter 5 occurred and addressing limitations of the current model.

6.1 Causes of Death

In this model, the patients could die from tumor death, secondary cancer death, and normal death. The model did not include the risk of tumor death due to cardiac or pulmonary complications. The risk of pulmonary death was included in Lundkvist *et al*'s cost-effectiveness study because the chest was irradiated during treatment for medulloblastoma.[19] For LGG treatment, no chest irradiation is expected and thus the risk of pulmonary complications is small. The risk of cardiac death could be significant as studies have shown that pediatric brain tumor patients have an excess risk of obesity, which could lead to diabetes and heart problems. Future health and cost effectiveness studies should analyze obesity and cardiac complications in more detail.

For each simulation, the wide distribution in total cost incurred by each patient can be explained by the risks of death. Patients who died early only had a low total cost from long-term effects (especially due to IQ loss). Patients who died later had a higher total cost, especially if they had an endocrine dysfunction or hearing loss as both of those health effects are associated with life-long recurring costs.

Proton therapy was more cost-effective in the base case as patients lived longer and were faced with more recurring costs. The base case applied death rates based on follow up studies of LGG patients specifically. [73] [42] Patients lived on average to age 70, at which time they had incurred the whole cost associated with IQ loss (the cost due to IQ loss was stopped after age 65). In the sensitivity analysis, death rates based on the Childhood Cancer Survivor Study (CCSS) for all pediatric tumors were applied. [34] The patients had a higher risk of death due to tumor complications and only lived to age 60, on average. Cost savings changed due to the difference in recurring costs from IQ loss, endocrine dysfunctions, and hearing loss.

6.2 IQ Loss

Since proton therapy provides a tighter dose distribution, it would be expected that the dose difference would result in a higher IQ loss for IMRT patients. However, the analysis of the patient treatment plans showed that there was only a small difference in IQ loss between proton therapy and IMRT. The results found that the calculated change in IQ score was almost the same for proton therapy and IMRT treatment plans. The difference in IQ loss between the two treatment plans was 2 points for P1 (17 points for proton therapy vs. 19 points for IMRT) and 1 point for P2 (16 points for proton therapy vs. 17 points for IMRT). When this phenomenon was further explored with P3 and P4, the difference in IQ loss was only 1 point between the two treatment modalities.

There are two possible explanations for this small difference in IQ loss. The first is that the model used to calculated IQ change may not be appropriate for the patient cases used. The breakdown between V_{0-30} and V_{30-60} may not be sensitive enough

for patients with only a small percentage of the supratentorial brain receiving doses of 30 Gy or higher. All cases had less than 50% of the supratentorial brain receiving 30-60 Gy. Furthermore, a more detailed version of Merchant *et al*'s IQ score model should be used to account for uncertainty in the IQ difference. Are the 1 or 2-point IQ difference found in the analysis of the patient treatment plans significant? If they are, then the results of this thesis indicate that there are significant potential savings from reducing the risk of IQ loss.

The second explanation is that, assuming Merchant *et al*'s method is correct, there really is not much of a difference in IQ loss from the way patient are currently treated. Since the protocol for designing proton therapy treatment plans did not call for sparing of the supratentorial brain, it is possible that the proton therapy plans used in this study were not optimized and thus did not result in a lower IQ loss when compared to IMRT.

As stated in Chapter 3, the reason for IQ loss is still unknown. Studies that correlate radiation therapy to IQ loss focus on the supratentorial brain or the temporal lobe. The study by Jalali et al found that patients had a higher risk of IQ loss if the left temporal lobe received a high dose. [92] Specifically, a dose of 43.2 Gy or higher to greater than 13% of the brain led to a higher chance of an IQ loss greater than 10 points. If Jalali *et al*'s finding were applied to P1, the risk of an IQ loss greater than 10 points would be 64% for both proton therapy and IMRT (Table 6.1)

Table 6.1: Risk of IQ Loss greater than 10 points based on P1's temporal lobe DVHs

	Left Temporal Lobe Receiving 43.2 Gy or higher	Risk
Proton Therapy	18.2%	64%
IMRT	54.6%	64%

For P2, the risk of acquiring an IQ loss greater than 10 points would be 19% for both proton therapy and IMRT (Table 6.2). The interesting connection between the results based on Jalali *el al*'s study and Merchant *et al*'s study is that there are still

no differences between the proton therapy and IMRT treatment plans in terms of IQ loss risk. Further work should be conducted analyze the change in IQ based on proton therapy and IMRT treatment plans from several more pediatric LGG cases. If possible, a follow-up of the patients whose cases are analyzed should be done to determine if the calculated IQ loss matches with the actual IQ change.

Table 6.2: Risk of IQ Loss greater than 10 points based on P2's temporal lobe DVHs

	Left Temporal Lobe Receiving 43.2 Gy or higher (%)	Risk
Proton Therapy	2.6%	19%
IMRT	12.9%	19%

The cost associated with IQ loss was the largest contributor to overall costs. Furthermore, IQ was the largest contributor to the difference in costs of long-term health effects between proton therapy and IMRT. The results of the P1 and P2 simulations show an average cost difference from IQ loss of ~$14,000/IQ point, as shown in Table 6.3.

Table 6.3: Average costs from IQ loss, IQ cost difference, and IQ points difference comparison for P1 and P2

Case	IQ Points Loss	Avg. Cost of IQ Loss ($)	Cost Difference ($)	IQ Points Difference ($)	Cost/IQ Point ($)
P1 IMRT	19	275,000	29,000	2	14,500
P1 PT	17	246,000			
P2 IMRT	17	246,000	14,000	1	14,000
P2 PT	16	232,000			

No patients in the model had an IQ score below the threshold of 70 points for special education; hence, there was no special education costs associated with the P1 and P2 analysis. Based on a $15,000/student cost of special education and a discount rate of 3%, the special education cost of a child attending school from age 5-18 can amount up to $159,524. A difference between proton therapy and IMRT

in the population needing special education could lead to very high cost savings. However, the costs of special education could be underestimated, as the 70 points threshold is not a hard guideline for children receiving special education. Children treated with radiation therapy for brain tumors have a high likelihood of requiring special education. A 10-year follow-up study of patients treated for medulloblastoma found that 80% of the cohort received special education.[93] The data from the MGH follow-up of proton pediatric patient shows that about 50% of the cohort received special education.[94] Since LGGs are benign tumors, the tumor and treatment are usually not as aggressive as some of the others CNS tumors. Hence it is expected that the student need for special education in patients treated for LGGs should be less than found in the MGH study (which included all types of tumors) and the Hirsch-Hopper *et al* childhood medulloblastoma study. However, more studies are needed to determine the extent to which LGG pediatric patients receive special education.

6.3 Endocrine Dysfunctions, Hearing Loss, and Secondary Cancer

There was a lower incidence of GHD, hypothyroidism, hearing loss, and secondary cancer from proton therapy compared to IMRT. However, the reduced incidence of those long-term health effects was not the main factor in making proton therapy cost-effective. This result is in part due to the relative low cost associated with those health effects compared to the cost of IQ loss and in another due to limitations of the model.

Hypothyroidism was the second most common long-term health effect; this occurred in ~55% of all IMRT patients and ~33% of all proton therapy patients. The thyroid dysfunction can lead to a number of subsequent health effects, such as diabetes and cardiac disease. However, the cost difference from hypothyroidism between proton therapy and IMRT was less than $1,000/patient in both the P1 and P2 case. The costs of hypothyroidism from this model do not translate well into the full costs

of the disease as the cost from complications that could occur if hypothyroidism was not treated (such as diabetes) was not included. Furthermore, hypothyroidism is a condition that afflicts a patient throughout their whole life, affecting their quality of life in ways that cannot be quantified monetarily.

GHD was the third most common long-term health effect, with ~43% of all IMRT patients and ~32% of all proton therapy patients needing growth hormone replacement. The costs savings from GHD were the second highest after IQ loss savings. The cost savings associated with GHD from proton therapy was $12,000/patient for both P1 and P2. The similarity in costs between the two cases reflected the model design, assigning a set probability of acquiring GHD at 35% for proton therapy and 48% for IMRT. The sensitivity analysis showed that the cost of GHD had a significant influence on the overall cost-effectiveness of proton therapy. Since the cost of GHD occurs early after treatment, the cost is not as discounted when compared to lifetime costs incurred from IQ loss and hypothyroidism. Since the yearly costs of growth hormone treatment are high (ranging from $5,000-$30,000), the higher cost of GHD means that any reduction in the incidence of GHD from proton therapy will results in a higher cost difference.

Growth hormone therapy is usually stopped after children reach their final height. However, some childhood cancer survivors remain growth hormone deficient into adulthood. Gleeson *et al* studied a group of 74 childhood cancer survivors treated with radiation therapy to determine the incidence of GHD at their final height. The study found that 64% of the survivors who were treated with growth hormone as children again tested positive for GHD.[57] The cost of GHD would be higher if treatment into adulthood was included. However, the majority of the costs would still come from childhood GHD treatment as adults only receive a 10th of the dose administered to children.

There was no risk of hearing loss based on all treatment plans except for P2's IMRT treatment plan. The dose to the cochlea was high enough to provide a risk of 0-16% for hearing loss. This finding is not surprising based on the tumor site for P1 and P2. P1's tumor is an astrocytoma located near the central region of the brain

and away from the left and right cochleas. P2's posterior fossa tumor is closer to both cochleas, which makes the structures more likely to receive a significant dose from IMRT, as seen in Appendix A.

In the case when hearing loss occurred, the average lifetime cost was significant at ~$7,000/patient. However, that value reflects the cost of hearing loss mitigation and does not indicate the true cost of hearing loss to an individual. The maximum cost an individual can accumulate from having a hearing loss from age 5 to age 70 is $20,000. It is possible that having a hearing disability leads to fewer job opportunities and a certain level of income loss, which was not reflected in the model. Furthermore, studies have shown that children and adults with hearing loss report a lower quality of life. [95] [96] There are psychological and well-being costs associated with hearing loss that are not accounted for in this model and could make proton therapy even more cost effective.

The overall risk of secondary cancer was 2% with proton therapy and 3% with IMRT. These findings are in line with the risks of secondary cancers from childhood tumors found in literature. Researchers from St. Jude Children's Research Hospital found a 4% risk of secondary cancer 15 years after treatment from a follow-up study of 1,283 pediatric patients treated for CNS tumors.[66] The study found a 0.4% risk of secondary cancer for patients with LGGs as their primary tumor. The model presented here could have overestimated the risk of secondary cancer as the risks used in the simulations were taken from the Winkfield *et al* study, which calculated the risks of secondary cancer from treatment of adult brain tumors. A study of secondary cancers after pediatric tumors from a population in the United Kingdom found a 25-year secondary risk of 4.2%. The Childhood Cancer Survivor Study (CCSS) found a 30-year secondary cancer risk of 9% for pediatric patients.[64] Though the CCSS followed a large cohort of pediatric patients ($n = 14,361$), the study involved all types of cancers, which have various degrees of malignancy and have higher incidences of secondary cancer than LGGs.

In the P1 and P2 simulations, the costs associated with secondary cancers were negligible (less than $1,000). Even though the cost savings from secondary cancer

is low for proton therapy, the importance of the reduction of secondary cancer cases cannot be disregarded. First of all, the model might have underestimated the cost associated with secondary cancer. The model limited risk of secondary cancers that could occur in a patient's lifetime, stopping the risk of acquiring a secondary cancer at 15 years after treatment, since reliable data beyond that time was not available. Second, it was assumed that the cost of treatment only occurred that year, though it is possible that the treatment of the secondary cancer resulted in additional long-term health effects not accounted for in this model. There is a need for longer follow-up studies of pediatric cancer survivors who were treated with proton therapy to evaluate the true lifetime risk. Finally, the psychological cost of acquiring a secondary cancer is difficult to measure, and more studies on the quality of life of patient with secondary cancers should be performed.

Proton therapy could prove to be even more health and cost effective when compared to IMRT. Each long-term health effect could result in a higher total cost than those found in this thesis if the additional factors described in this chapter are accounted for. There is a need for more studies evaluating the dose effects of radiation on the risks of long-term health effects to determine the magnitude to which proton therapy is more health effective than photon therapy. The costs associated with IQ loss and GHD were found to be the main drivers of the total cost difference between proton therapy and IMRT, and further studies should investigate the impact of those health effects on their costs the patient and society.

Chapter 7

Conclusions

This thesis proposes a method for the comparison of long-term health effects and costs for proton therapy and IMRT as treatment for pediatric brain tumors. The method was applied to two pilot cases, P1 and P2. The risk of IQ loss and hearing loss was calculated from each patients dose-volume histograms, using models that relate radiation dose to the risk of long-term health effects. [42] [44] A review of the literature was performed to determine the health risks of GHD, hypothyroidism, and secondary cancers and the costs associated with the long-term health effects. A Markov simulation model was developed the estimate the health and cost effectiveness of proton therapy based on those risks.

The analysis of the treatment plans showed that there was not a large difference in IQ loss and hearing loss between proton therapy and IMRT for the two patients in the pilot study. However, the treatment plans are influenced by the location and size of the tumor as well as the field arrangements. It is possible that more significant differences between the proton therapy and IMRT dose-volume histograms could be observed using other patients data, which would result in higher differences in IQ loss and hearing loss. There a higher difference in the incidence of GHD and hypothyroidism. In the model simulations, the use of IMRT treatment resulted in a higher number of patients with health complications, with the number of additional cases per 100 patients at 11 and 23 for GHD and hypothyroidism. Two additional patient treatment plans (P3 and P4) were analyzed to investigate the unexpected

small difference in IQ loss between the two treatment modalities found using P1 and P2's treatment plans. The difference in IQ loss between proton therapy and IMRT was only 1 IQ point for both patients.

When the Markov simulations were run based on P1 and P2s health risks, proton therapy was more cost effective due to the difference in costs associated with IQ loss and GHD. IQ loss and GHD were also the main contributors to total costs accumulated by the patients in the simulations. The cost difference associated with IQ loss was equal to about \$14,000/IQ point per patient for their entire life. Since the cost associated with IQ loss is the driver of high total cost and high cost difference between proton therapy and IMRT, this finding suggests that treatment cases where proton therapy leads to a lower degree of IQ loss would make proton therapy more cost-effective. Further studies should evaluate the impact of proton therapy on IQ loss in more details.

The total costs associated with GHD were sensitive to the cost of growth hormone treatment. Since growth hormone is expensive and children require a high dose, the yearly cost of growth hormone therapy ranges from \$5,000 to greater than \$30,000. When the Markov model is run with higher yearly costs of growth hormone treatment, the difference in costs due to GHD was \$40,000/patient for the P1 and P2 simulations. As the dose of growth hormone required depends on the patients weight, heavier children will incur higher costs. Long-term childhood cancer survivors tend to have a higher relative weight compared to their peers without cancer and would be faced with higher growth hormone costs.

If the cost savings due to IQ loss are not considered, since that cost represents unrealized earning potential as opposed to paying for treatment, proton therapy is more expensive than IMRT by \$12,000/patient in the P1 simulation and \$5,000/patient in the P2 simulation. However, this result does not mean that proton therapy should not be used as a treatment for pediatric brain tumors. Though hypothyroidism, hearing loss, and secondary cancers were not associated with a high cost difference between the two treatment modalities, the reduction in the incidence of each health-effect provides a strong case for the use of proton therapy for the treatment of pediatric

brain tumors. Furthermore, the cost results may not reflect the total cost incurred from long-term health effects:

1. There are additional costs associated with each of the long-term health effects that are not reflected in this model (for example, the cost of cardiac disease from thyroid hormone deficiency). The inclusion of those costs in future work could indicate an even higher degree of cost-effectiveness using proton therapy, even in the case if proton therapy is not as health effective, as presented in this thesis.

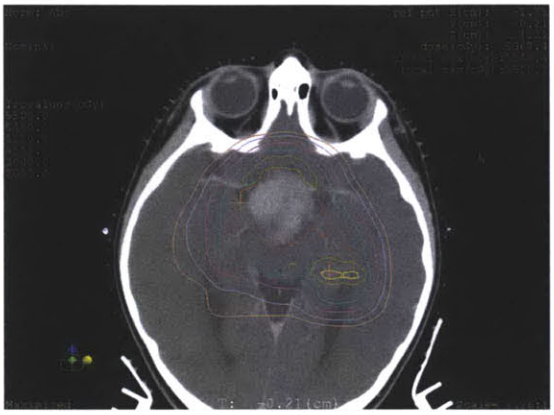
2. The burden of long-term health effects materialize in ways that monetary costs alone cannot represent.

This thesis provides the framework and computational tools for further analysis. Stakeholders should not use the results from the limited simulations based on P1 and P2s health risks to make the decision about using proton therapy over IMRT (or vice-versa). Rather, they should use the method described in this thesis to further investigate the long-term health effects and costs of both treatment modalities. Future work should apply the analysis method of this thesis to more patient treatment plans. As treatment plans vary from one patient to another, this future work can help determine the extent to which proton therapy and IMRT treatment plans differ in practice and whether this difference provides a lower risk of long-term health effects by using proton therapy. The estimated risk parameters should then be used in the Markov model to determine whether proton therapy or IMRT is more effective in the treatment of pediatric brain tumors and other solid cancers.

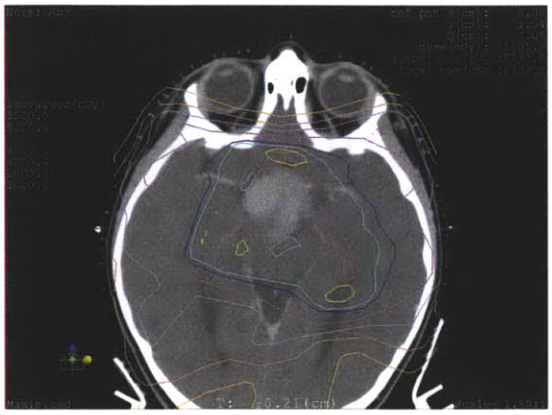
Appendix A

Patient Treatment Data

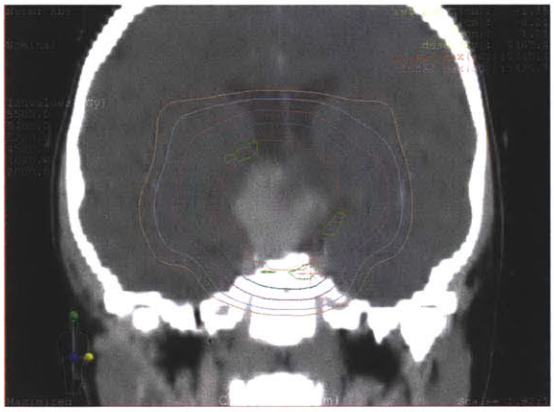
Appendix A provides additional images and DVHs from each of the patient treatment plans. The images are pictures of the P1 and P2 treatment plans in XiO®, in the axial, sagittal, and coronal views. The GTV is contoured in red. The other lines represent the isodose lines. DVHs of the whole brain, supratentorial brain, left cochlea, and right cochlea are shown for P1, P2, P3, and P4.



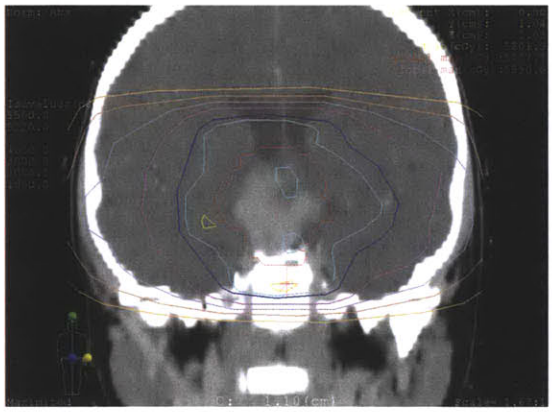
(a) Proton therapy - axial view



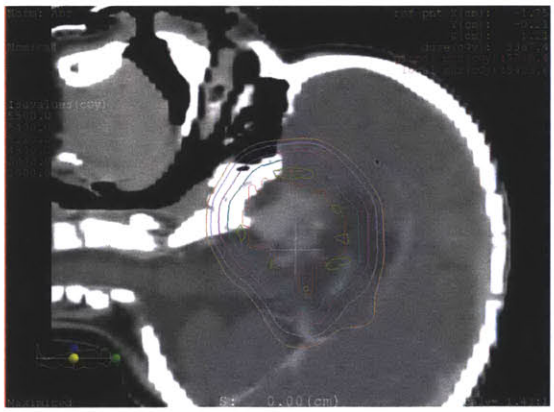
(b) IMRT - axial view



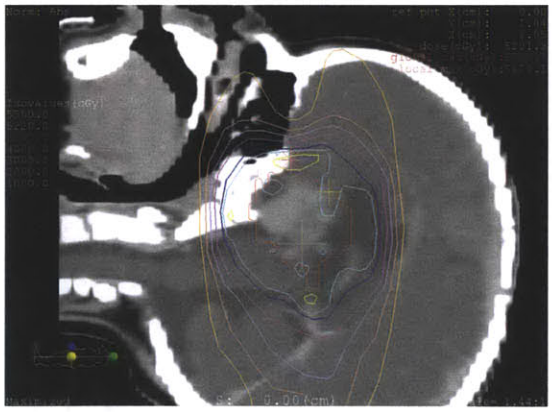
(c) Proton therapy - coronal view



(d) IMRT - coronal view



(e) Proton therapy - sagittal view



(f) IMRT - sagittal view

Figure A-1: Proton therapy and IMRT treatment plans for P1, as seen from the axial, sagittal, and coronal views. The red contour line delineates the GTV.

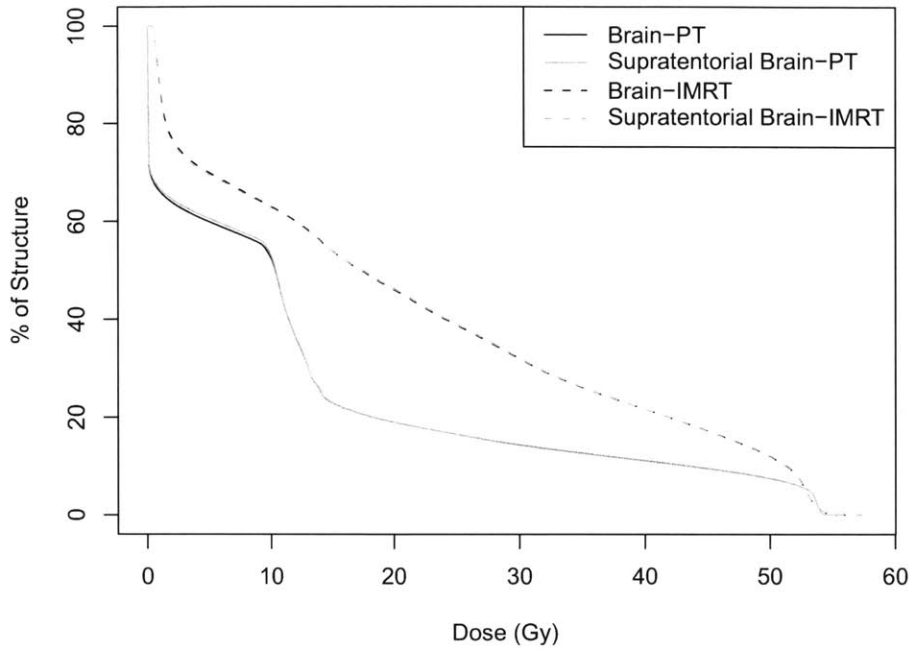


Figure A-2: P1 DVHs of the brain and supratentorial brain from proton therapy and IMRT treatment plans

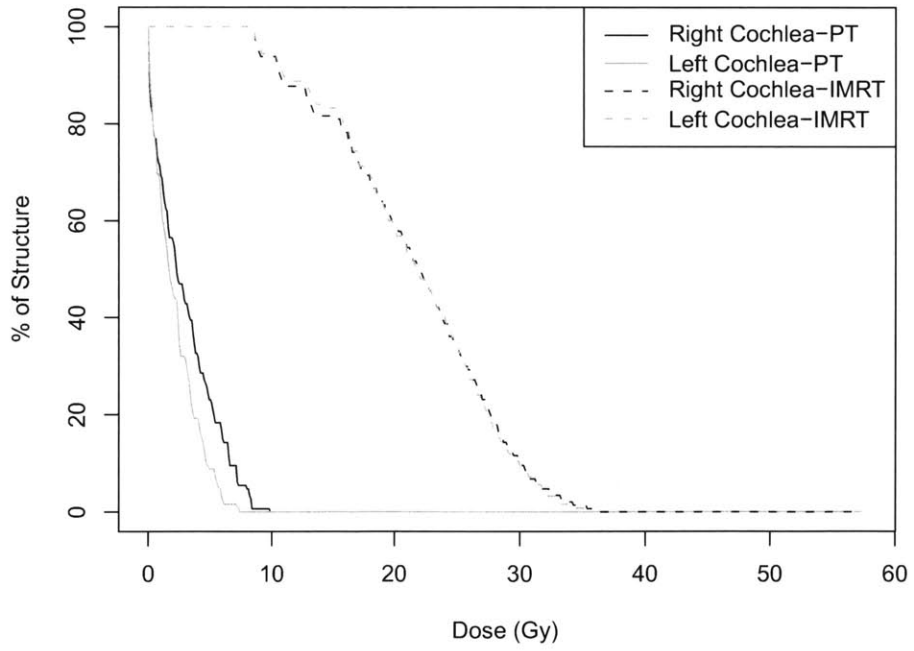
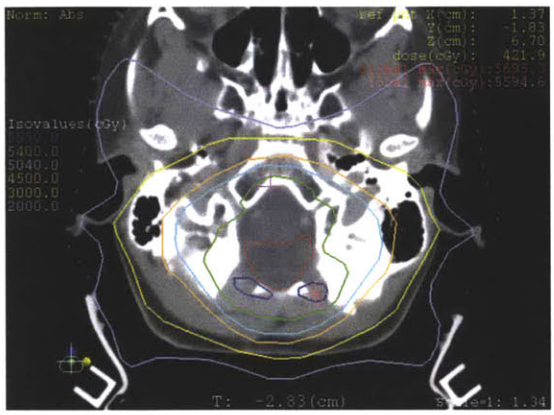
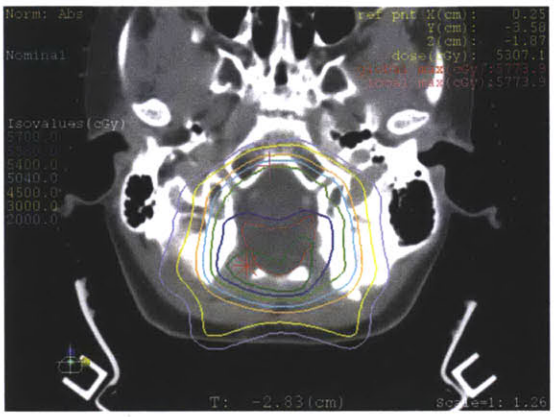


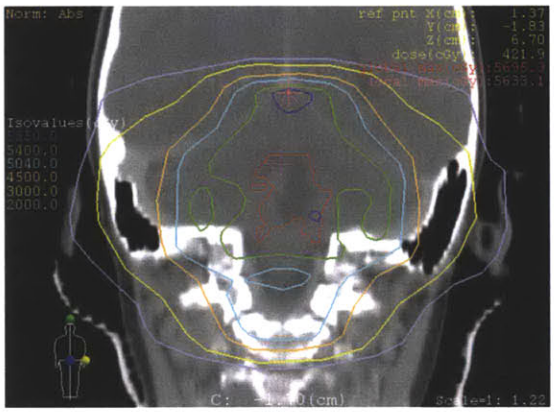
Figure A-3: P1 DVHs of the left and right cochleas from proton therapy and IMRT treatment plans



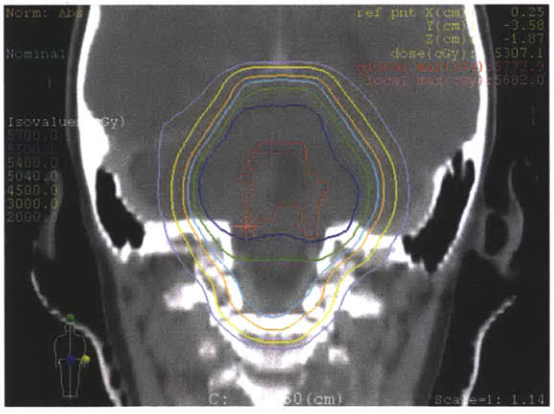
(a) Proton therapy - axial view



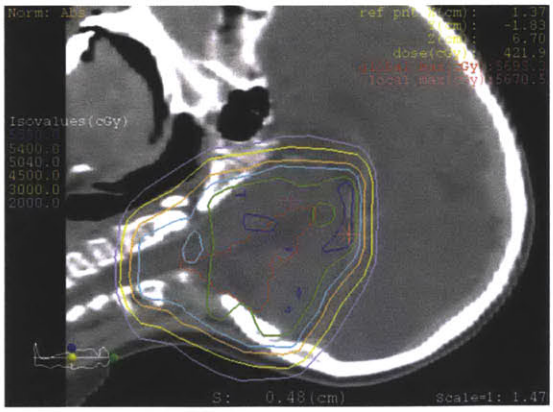
(b) IMRT - axial view



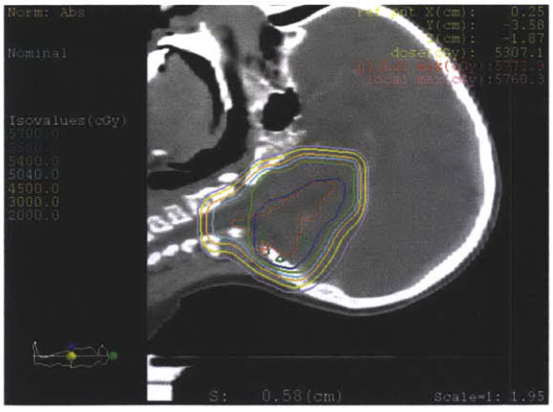
(c) Proton therapy - coronal view



(d) IMRT - coronal view



(e) Proton therapy - sagittal view



(f) IMRT - sagittal view

Figure A-4: Proton therapy and IMRT treatment plans for P2, as seen from the axial, sagittal, and coronal views. The red contour line delineates the GTV.

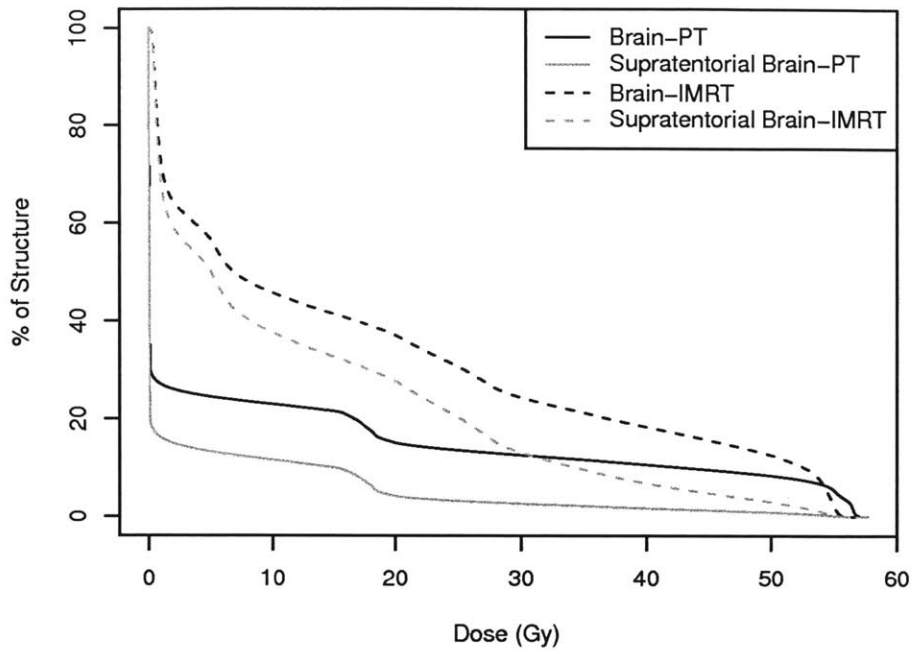


Figure A-5: P2 DVHs of the brain and supratentorial brain from proton therapy and IMRT treatment plans

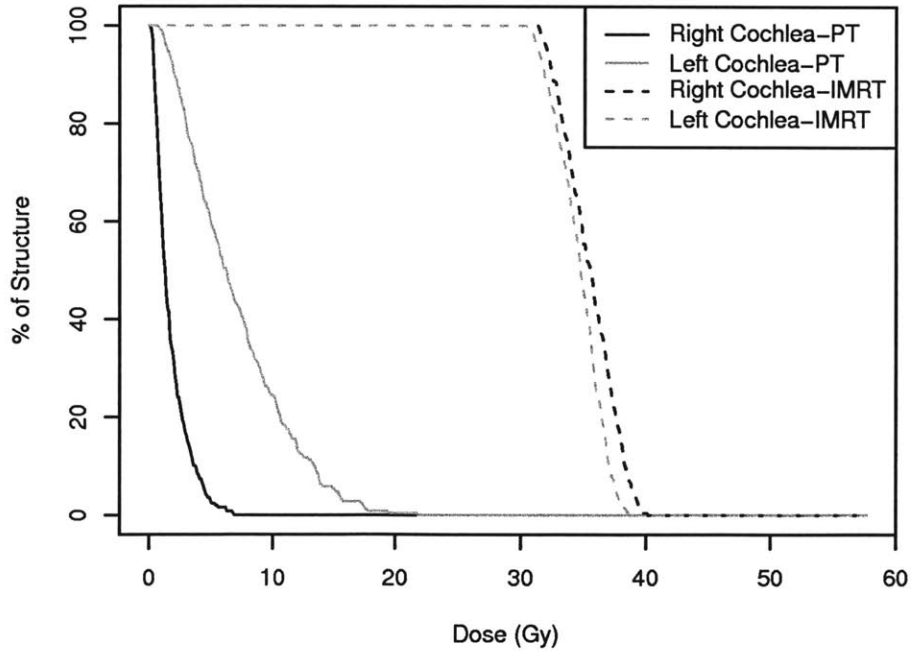


Figure A-6: P2 DVHs of the left and right cochleas from proton therapy and IMRT treatment plans

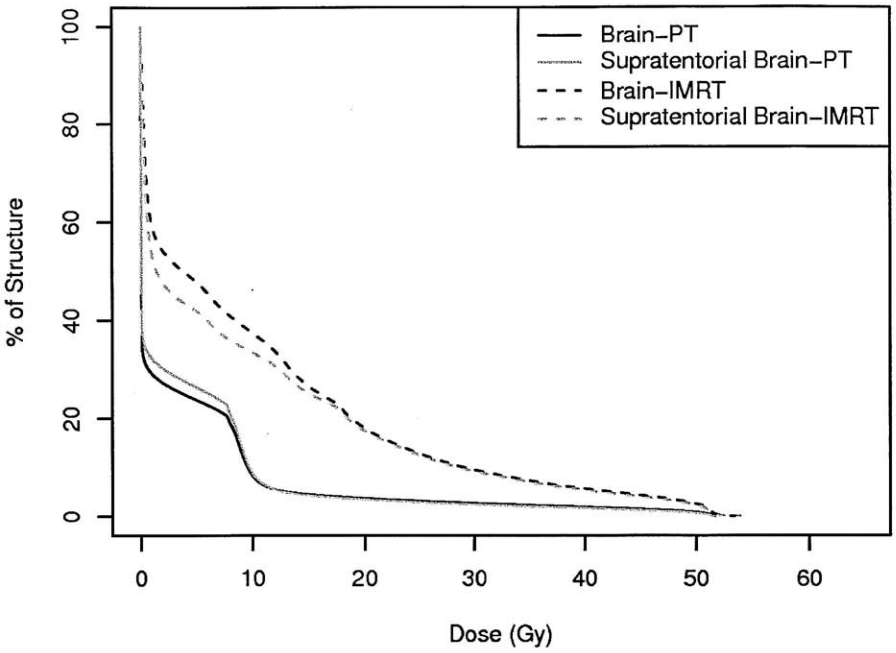


Figure A-7: P3 DVHs of the brain and supratentorial brain from proton therapy and IMRT treatment plans

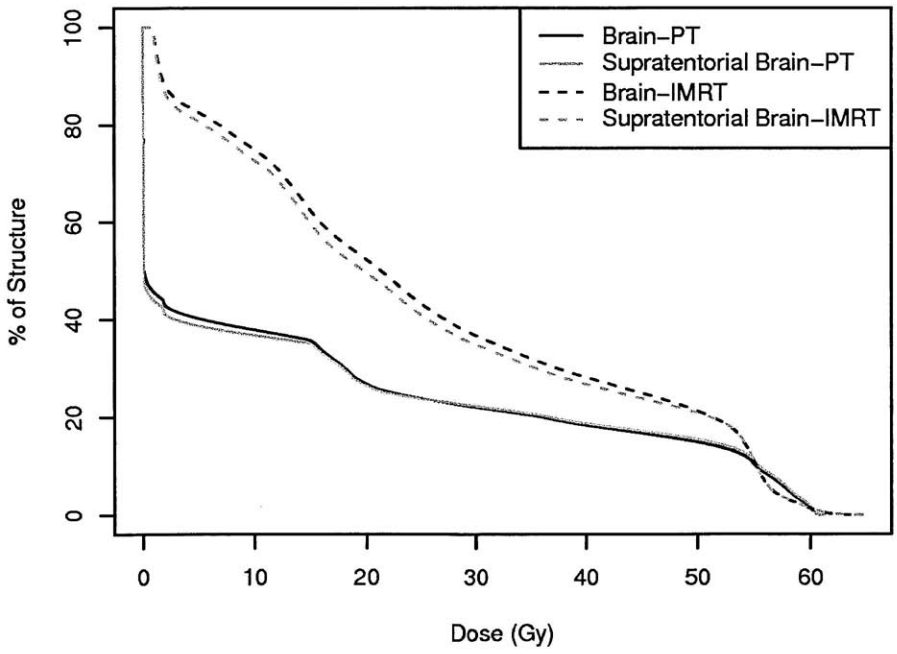


Figure A-8: P4 DVHs of the brain and supratentorial brain from proton therapy and IMRT treatment plans

Appendix B

Risk and Cost Tables

Appendix B contains the detailed risk and cost tables used in the Markov model. The risks and costs where determined based on age, gender, and/or cycle period. The cycle period was used to assign risks and costs for events that depended on time after treatment as opposed to age of the patient.

Probability of event and rate of event were related by the equations:

$$\mathrm{p(t)} = 1 - e^{-rt} \tag{B.1}$$

and

$$\mathrm{r(t)} = -[ln(1 - p(t))]/t \tag{B.2}$$

where p(t) is the probability at time t, r is the rate at which the event occurs (number of events per population-time), and t is time during which the event can occur.

Table B.1: Yearly probability of Normal Death based on 2006 US Life Charts

Age	Male	Female	Age	Male	Female	Age	Male	Female
1	0.000460	0.000427	34	0.001589	0.000829	67	0.019974	0.012855
2	0.000322	0.000276	35	0.001653	0.000893	68	0.021630	0.014010
3	0.000245	0.000185	36	0.001737	0.000967	69	0.023559	0.015359
4	0.000195	0.000162	37	0.001851	0.001057	70	0.025737	0.016895
5	0.000186	0.000149	38	0.002001	0.001166	71	0.028223	0.018652
6	0.000176	0.000134	39	0.002183	0.001293	72	0.031103	0.020679
7	0.000163	0.000123	40	0.002381	0.001425	73	0.034372	0.022999
8	0.000139	0.000111	41	0.002592	0.001563	74	0.037995	0.025637
9	0.000107	0.000099	42	0.002827	0.001713	75	0.042023	0.028641
10	0.000081	0.000091	43	0.003087	0.001877	76	0.046338	0.031894
11	0.000083	0.000093	44	0.003369	0.002052	77	0.051072	0.035502
12	0.000136	0.000113	45	0.003662	0.002236	78	0.056262	0.039502
13	0.000254	0.000155	46	0.003970	0.002425	79	0.061944	0.043932
14	0.000418	0.000211	47	0.004309	0.002617	80	0.068159	0.048833
15	0.000594	0.000275	48	0.004694	0.002812	81	0.074947	0.054251
16	0.000759	0.000334	49	0.005125	0.003020	82	0.082352	0.060231
17	0.000918	0.000382	50	0.005602	0.003247	83	0.090417	0.066824
18	0.001063	0.000414	51	0.006107	0.003497	84	0.099186	0.074082
19	0.001193	0.000434	52	0.006617	0.003773	85	0.108704	0.082058
20	0.001329	0.000453	53	0.007104	0.004070	86	0.119015	0.090810
21	0.001456	0.000475	54	0.007570	0.004383	87	0.130161	0.100392
22	0.001536	0.000494	55	0.008042	0.004710	88	0.142182	0.110863
23	0.001554	0.000508	56	0.008550	0.005061	89	0.155116	0.122277
24	0.001526	0.000519	57	0.009114	0.005457	90	0.168995	0.134688
25	0.001480	0.000532	58	0.009781	0.005928	91	0.183844	0.148146
26	0.001443	0.000546	59	0.010582	0.006494	92	0.199686	0.162697
27	0.001416	0.000562	60	0.011543	0.007183	93	0.216530	0.178377
28	0.001408	0.000580	61	0.012632	0.007966	94	0.234379	0.195216
29	0.001418	0.000604	62	0.013798	0.008781	95	0.253223	0.213232
30	0.001437	0.000634	63	0.014946	0.009551	96	0.273043	0.232430
31	0.001460	0.000671	64	0.016067	0.010282	97	0.293803	0.252802
32	0.001500	0.000718	65	0.017272	0.011073	98	0.315457	0.274321
33	0.001535	0.000769	66	0.018518	0.011885	99	0.337943	0.296944
						100	1.000000	1.000000

Table B.2: Yearly probability of death due to tumor recurrence in the base case

Cycle	Probability
1	0.0030
2	0.0030
3	0.0030
4	0.0030
5	0.0030
6	0.0098
7	0.0041
8	0.0041
9	0.0040
10	0.0040
11	0.0445
12	0.0074
13	0.0073
14	0.0073
15	0.0072
16	0.0072
17	0.0071
18	0.0070
19	0.0070
20	0.0069
21+	0.0000

Table B.3: Yearly probability of death due to secondary cancer

Cycle	Probability
1-14	0.0012
15-19	0.0013
20-24	0.0017
25-29	0.0023
30-34	0.0046
35+	0.0000

Table B.4: Yearly probability of death due to tumor recurrence in the sensitivity analysis

Cycle	Value
1	0.0030
2	0.0030
3	0.0030
4	0.0030
5-9	0.0080
10-14	0.0090
15-19	0.0100
20-24	0.0110
25-29	0.0120
30-34	0.0130
35+	0.0000

Table B.5: Yearly costs associated with IQ loss

Age	Male IQ Cost	Female IQ Cost
1	$0	$0
2	$0	$0
3	$0	$0
4	$0	$0
5-19	$15,000	$15,000
19-65	$878	$1,146
65+	$0	$0

Table B.6: Yearly costs associated with GHD by age based on the 50th percentile weight of the U.S. population

Age	Cost Male	Cost Female
1	N/A	N/A
2	$5,803	$5,539
3	$6,589	$6,329
4	$7,472	$7,201
5	$8,437	$8,155
6	$9,445	$9,186
7	$10,511	$10,333
8	$11,690	$11,658
9	$13,046	$13,208
10	$14,629	$14,975
11	$16,473	$16,874
12	$18,573	$18,759
13	$20,861	$20,459
14	$23,188	$21,838
15	$25,347	$22,840
16	$27,145	$0
17+	$0	$0

Table B.7: Yearly costs associated with GHD by age based on the 75th percentile weight of the U.S. population

Age	Cost Male	Cost Female
1	N/A	N/A
2	$6,254	$5,989
3	$7,141	$6,911
4	$8,156	$7,935
5	$9,279	$9,051
6	$10,462	$10,266
7	$11,726	$11,639
8	$13,145	$13,248
9	$14,796	$15,134
10	$16,725	$17,259
11	$18,934	$19,498
12	$21,370	$21,659
13	$23,926	$23,539
14	$26,441	$24,992
15	$28,723	$0
16	$30,611	$0
17+	$0	$0

Table B.8: Yearly Risk of GHD

Cycle	Proton Therapy	IMRT
1	0.0422	0.0649
2	0.0404	0.0607
3	0.0387	0.0568
4	0.0371	0.0531
5	0.0355	0.0496
6	0.0340	0.0464
7	0.0326	0.0434
8	0.0312	0.0406
9	0.0299	0.0379
10	0.0286	0.0355
11+		0.0000

Table B.9: Yearly Risk of Hypothyroidism

Cycle	Proton Therapy	IMRT
1	0.0422	0.1077
2	0.0404	0.0961
3	0.0387	0.0857
4	0.0371	0.0765
5	0.0355	0.0683
6	0.0340	0.0609
7	0.0326	0.0544
8	0.0312	0.0485
9	0.0299	0.0433
10	0.0286	0.0386
11+		

Table B.10: Yearly Risk of Secondary Cancer

Cycle	Proton Therapy	IMRT
1-15	0.00120	0.00184
16+	0.00000	0.00000

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