Modeling secondary cancer risk following paediatric radiotherapy: a comparison of intensity modulated proton therapy and photon therapy

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Abstract

Proton radiotherapy is known to reduce the radiation dose delivered to normal healthy tissue compared to photon techniques. The increase in normal tissue sparing could result in fewer acute and late effects from radiation therapy. In this work proton therapy plans were created for patients previously treated using photon therapy. Intensity modulated proton therapy (IMPT) plans were planned using inverse planning in Varian®’s Eclipse™ treatment planning system with a scanning proton beam model to the same relative biological effectiveness (RBE)-weighted prescription dose as the photon plan. Proton and photon plans were compared for target dose conformity and homogeneity, body volumes receiving 2 Gy and 5 Gy, integral dose, dose to normal tissues and second cancer risk. Secondary cancer risk was determined using two methods. The relative risk of secondary cancer was found using the method described by Nguyen et al.¹ by applying a linear relationship between integral dose and relative risk of secondary cancer. The second approach used Schneider et al.’s organ equivalent dose concept² to describe the dose in the body and then calculate the excess absolute risk and cumulative risk for solid cancers in the body.

IMPT and photon plans had similar target conformity and homogeneity. However IMPT plans had reduced integral dose and volumes of the body receiving low dose. Overall the risk of radiation induced secondary cancer was lower for IMPT plans compared to the corresponding photon plans with a reduction of ~36% using the integral dose model and ~50% using the organ equivalent dose model.

Résumé

Un avantage connu de la radiothérapie par protons est la réduction de la dose reçue par les tissus normaux et sains par rapport aux traitements en photons. Cette réduction de dose peut résulter en une diminution des effets aigus et tardifs de la radiothérapie. Dans cet ouvrage, les plans de protonthérapie ont été créés pour des patients ayant été traités par radiothérapie en photons. Les plans de protonthérapie conformationnelle avec modulation d’intensité (PCMI) ont été conçus par planification inverse dans le système de planification de traitement Eclipse™ de Varian® de façon à ce que le faisceau de protons en balayage produise la même dose de prescription que plan en photons, tout en tenant compte des efficacités biologiques relatives des deux types de radiation. Les plans en photons et en protons ont ensuite été comparés en termes de conformité de la dose, d’homogénéité de la dose, de volumes recevant 2 et 5 Gy, de dose intégrale, de dose aux tissus normaux et de risque de cancer secondaire. Le risque relatif de cancer secondaire a été déterminé par la méthode décrite par Nguyen et al.3 en appliquant une relation linéaire entre la dose intégrale et le risque relatif de cancer secondaire. Une deuxième approche employée dans cet ouvrage utilise le concept de dose équivalente à un organe de Schneider et al.4 pour décrire la dose dans le corps et par la suite calculer l’excès de risque absolu et le risque cumulatif de cancers solides dans le corps.

Les traitements comparés, soit en photons et en protons, ont démontré une conformité et une homogénéité de la dose similaires dans le volume cible. Toutefois, les plans de PCMI réduisent la dose intégrale et diminuent les volumes du corps recevant une faible dose. Globalement, le risque d’induction d’un cancer secondaire est plus faible pour les plans de PCMI que pour les plans équivalents en photons avec une réduction de ~36% en utilisant le modèle de dose intégrale et ~50% en utilisant le modèle de dose équivalente à un organe.

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Since the discovery of x-rays by Roentgen in 1895, ionizing radiation has been used in the treatment of cancer, and it is now a major component in the treatment of many cancers. In 2010 173,800 new cases of cancer were diagnosed and 76,200 deaths were attributed to cancer in Canada(1). Of these newly diagnosed patients approximately 60% were treated with radiation therapy either alone or in combination with another form of treatment such as chemotherapy or surgery(1).

1.1 Paediatric Cancers and the Role of Radiotherapy

Approximately 0.7% of the new cancer cases diagnosed in 2010 were in children. Cancer survival rates in children have continued to rise because of improvements in surgery, chemotherapy and radiotherapy techniques: the standard treatment modalities. Currently, paediatric cancers have a 5 year survival rate of approximately 82%(1).

Cancers experienced in childhood are different than those in adults. Twenty to twenty-five percent of all paediatric malignancies are Central Nervous System (CNS) tumours. CNS tumours treated with radiotherapy include low and high grade astrocytomas, gliomas, ependymomas, craniopharyngiomas and medulloblastomas. Treatment for most CNS malignancies is tumour resection followed by radiation with or without adjuvant chemotherapy. If the tumour is inoperable or resection is incomplete, radiotherapy is used. In very young children chemotherapy may be used prior to radiotherapy(2).

Radiotherapy is also used to treat paediatric cancers outside the CNS. These include rhabdomyosarcoma, Wilms’ tumour, Ewing’s tumour, neuroblastoma and Hodgkin’s and non-hodgkin’s lymphoma. Rhabdomyosarcoma is the most common soft tissue cancer in children and can occur anywhere in the body. In most sites, treatment is a combination of either surgery and radiotherapy or chemotherapy and radiotherapy(2). Wilms’ tumour or nephroblastoma is the most common renal tumour in childhood. It is most commonly
treated with surgery, but if a patient is diagnosed with stage III or recurrent disease the patient is treated with radiotherapy following surgery(2). Ewing’s tumour is the second most common childhood bone cancer and is primarily treated with chemotherapy. Following chemotherapy, radiotherapy may be used in order to spare the limb. Neuroblastoma is a tumour located anywhere in the sympathetic nervous system and is the most common malignancy diagnosed before the age of one. It is most commonly treated with surgical resection; however radiotherapy may be used when there is lymph node involvement. Lympomas, Hodgkin’s and non-Hodgkin’s, are the third most common childhood cancer. In children, Hodgkin’s lymphoma is more common than non-Hodgkin’s lymphoma. Hodgkin’s lymphoma is usually treated with chemotherapy with low-dose radiotherapy to the involved field while non-Hodgkin’s lymphoma is treated with chemotherapy, and radiotherapy is only used for emergency treatments for mediastinal disease and palliation(2).

1.2 Modern Radiotherapy Techniques

1.2.1 3D Conformal Radiotherapy (3D-CRT)

The goal of radiotherapy is to uniformly treat the tumour volume with high dose while sparing healthy tissue. According to the International Commission on Radiation Units and Measurements (ICRU) Report No. 50(3), the dose distribution within the target should vary between -5% to +7% of the prescribed dose. Treatments based on three-dimensional anatomical information allow better target delineation and more conformal dose distributions(4). The treatment technique referred to as three-dimensional conformal radiotherapy (3D-CRT) employs 3D anatomical information for all aspects of treatment planning. The gross tumour volume (GTV), the visible or palpable extent of the tumour; clinical target volume (CTV), the GTV plus a margin for microscopic disease; planning target volume (PTV), the CTV plus a margin that accounts for uncertainties in contouring, machine tolerances and target motion; and organs at risk (OAR) are delineated on a 3D anatomical image, usually using a CT scan. These 3D images are used for treatment planning in a computerized treatment planning system. The plan is created in a technique known as forward planning in which all parameters for treatment
including couch, gantry, and collimator angles are selected; field size, MLC settings, wedges, beam energy, and beam weighting are set by trial and error by the planner(4). A 3D dose distribution is calculated using a computer algorithm that takes the patients 3D anatomy into account(5). The resulting treatment concentrates dose to the target volume while sparing normal surrounding tissue.

1.2.2 Intensity Modulated Radiation Therapy

Intensity modulated radiation therapy (IMRT) is a more advanced technique of 3D-CRT. Unlike 3D-CRT, which delivers a uniform fluence to the target from each beam, IMRT delivers a non-uniform fluence from each beam. The combination of all the beams results in a homogenous dose distribution to the target. IMRT requires a computer system that can calculate non-uniform fluence maps for multiple beams from various directions in order to maximize dose in the target while sparing surrounding normal tissue.

Treatment plans are created in a method called inverse planning. The planner selects the beam energy, orientation and dose objectives for the target and critical structures. The treatment planning system divides each beam into beamlets, and an optimization algorithm is used to calculate the optimal intensity of each beamlet in order to meet the specified plan criteria.

To deliver the plans, the treatment machine must be equipped with a system that can deliver intensity modulated beams such as a multileaf collimator, Tomotherapy® collimator or pencil beam scanning(4). The resulting dose distributions concentrate high dose in the target and minimize dose outside the target. However, IMRT results in larger volumes of the patient exposed to low doses(6).

1.2.1 Proton Therapy

Proton therapy is considered to be the most conformal radiation therapy technique. The use of a proton beam for radiotherapy was first suggested by Robert R. Wilson in 1946, however it was not until 1990 that the first hospital-based treatment facility was opened at Loma Linda University Medical Center(7). Proton beams have unique dose deposition characteristics that make them particularly advantageous for the treatment of paediatric tumours. Proton beams have a finite range and deliver the maximum dose at
the end of their range in what is called a Bragg Peak. Unlike photon beams, proton beams do not deposit dose distal to the target and also have a reduced entrance dose. Like IMRT, proton beam therapy delivers high dose to the target while sparing surrounding normal tissue. In contrast to IMRT, proton radiotherapy does not result in the deposition of low dose to large volumes of tissue. The difference in dose conformity is shown in Figure 1-1.

![3-D Conformal RT, IMRT and proton radiotherapy treatment plans.](image)

**FIGURE 1-1: Comparison of 3D-CRT, IMRT and proton radiotherapy treatment plans.** Green line (50.4 Gy), pink line (30 Gy), purple line (10 Gy). The 3D-CRT treats less volume of normal tissue than IMRT but to a higher radiation dose. The IMRT plan is highly conformal while treating a large volume to low dose. The proton plan is conformal and minimizes the volume treated to low dose(6).

There are two proton therapy delivery methods. The first, called passive scattering, laterally spreads the accelerated pencil beam to adequately cover the target. Patient specific apertures and compensators are used to shape the beam. The second, called spot scanning, scans the pencil beam over the target until Bragg peaks have been deposited throughout the target.

Proton therapy uses the same principles for treatment planning as photon therapy; however, because of the steep dose fall off at the end of the proton range, uncertainties in the CT based water-equivalent depths, beam ranges, patient set up, target position and motion are more important(4). Forward planning may be used for treatment planning of both scattered and scanning beams. Scanning beams may also be used for intensity modulated proton therapy (IMPT) in which the intensity of the beams hitting each spot are modulated. IMPT is also planned using inverse planning.

The benefit of proton therapy is the ability to treat tumours to high doses while sparing healthy tissue. The increase in normal tissue sparing results in fewer acute and
late effects from radiation therapy(8). The normal tissue sparing observed in proton therapy is currently being studied to see if it results in a reduction in acute and late effects from radiation treatment.

1.3 Risks Associated with Radiation Therapy

1.3.1 Acute Effects

A patient treated with radiotherapy may experience various side effects from treatment. The side effects may be acute or late effects. Acute effects occur during or immediately following treatment while late effects occur months or years after treatment. Tumour location, area and volume of normal tissue treated determine which acute effects a patient will develop. Acute effects include skin reddening, nausea, vomiting, heartburn, pneumonitis, fatigue and hair loss(7).

1.3.2 Late Effects

Late effects are those side effects that are absent at the end of treatment but develop months or years following treatment. Radiotherapy can cause damage in many organs and tissues. Cardiac effects include damage to the valves, pericardial thickening, heart disease and higher risk of angina and heart attack. Radiotherapy can cause sterility in men and infertility in women. In the bladder, radiation can induce fibrosis that decreases the bladder capacity and contractibility(9). The thyroid is particularly sensitive to radiation. Hypothyroidism is common after radiotherapy(10).

Late effects seen in children are particularly important because they are growing and may experience abnormal development. The patient may experience growth impairments from deficiencies in growth hormone production, early on-set puberty and under-development or incomplete development of tissues or organs, called hypoplasia, leading to asymmetric growth of tissues in and out of the radiation field(9). Radiation treatment to the brain can result in progressive decline in intellectual ability. Patients will not acquire knowledge and skills at an age-appropriate rate resulting in a progressive decline in IQ(2). Other intellectual deficits shown in children who have undergone cranial irradiation are reduction in attention, planning, memory and motor skills(10). Factors
affecting the severity of cognitive deficits are dose, irradiated volume and age. The most severe cognitive dysfunction is seen in young patients with large irradiated volumes treated to high dose(11). The pubertal development may also be affected by radiation therapy. Boys may have low testosterone or sterility while girls can have late puberty or infertility(9).

Radiation is useful in the treatment of cancers however it is a known carcinogen. The development of secondary malignancies following radiotherapy is a well-known effect. Leukemias arise 5-10 years after treatment while solid tumours have a latency period of 10-20 years(9). A secondary malignancy is a tumour that was not present at the time of initial treatment and has a different histology. The risk of the development of a secondary malignancy depends on the total volume irradiated, the dose and the volume irradiated to high doses(12). Radiation induced carcinomas typically develop in low and high dose areas(12). Radiation induced sarcomas usually arise in high dose regions often within the treatment beam(13). Children are at particular risk for the development of secondary malignancies because they are at least ten times more sensitive to radiation than adults(14).

The change in radiotherapy techniques has resulted in changes to the risk of acquiring a secondary cancer. In 2003, it was suggested by Hall et al(15) that the switch from 3D-CRT to IMRT increased the risk of secondary cancers due to the increase in volumes of the body receiving low doses and increased leakage and scattered doses. Hall also suggested that proton therapy could reduce the risk of secondary cancer but only when scanning proton therapy is used(14). Many planning studies have shown that proton therapy reduces the integral dose and improves dose distributions in OARs when compared with IMRT and 3D-CRT plans(16). A treatment plan comparison between IMRT, 3D-CRT and IMPT of a paediatric medulloblastoma patient performed by Miralbell et al(17) showed a fifteen-fold reduction in secondary cancer in the IMPT plan compared to the IMRT and 3D-CRT. Newhauser et al(18) also investigated the risk of secondary cancer after craniospinal irradiation. Taking into account therapeutic and stray radiation fields, the risk of secondary cancer for IMRT and 3D-CRT was 7 and 12 times the risk for a scanned proton therapy and 6 and 11 times the risk of passive scattering proton therapy. Reduction in secondary cancer risk using proton therapy versus photon
therapy was also shown for hepatocellular cancer(19), prostate cancer(20, 21) and paediatric rhabdomyosarcoma(17).

1.4 Purpose of Thesis and Outline
The aim of the study was to show that the risk of radiation-induced secondary cancers in paediatric patients is lower after IMPT compared to IMRT or 3D-CRT. Four steps were required to accomplish the goals of the project. First, IMPT treatment plans were created for patients previously treated using IMRT or 3D-CRT. Second, the plans were compared for target coverage, dose conformity, dose homogeneity, volumes of the body receiving low dose and integral dose. Third, the secondary cancer risk for proton and photon plans was determined using a method described by Schneider et al(22) and one based on the relationship between integral dose and relative risk of second cancer from Nguyen et al(23). Finally, the risk of secondary cancer after IMPT and IMRT or 3D-CRT was compared.

This thesis is organized into six chapters. The second chapter deals with the physics of photon and proton beams as well as treatment beam production and delivery. Chapter 3 describes the methods and materials used for patient selection, treatment planning and secondary risk calculation. IMPT treatment plans and their comparison to photon plans are presented and discussed in Chapters 4 and 5 respectively. Finally, Chapter 6 presents conclusions and recommendations for future work.

1.5 References


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Chapter 2:

Physics of Radiation Therapy

The physics describing proton and photon radiation therapy is discussed in the following chapter. The chapter includes a description of all the processes involved in the transfer of energy from ionizing radiation to the cells, which leads to cell death. This includes treatment beam production and delivery as well as particle interactions, stopping power, depth dose curves, lateral penumbra, relative biological effectiveness and absorbed dose.

2.1 Physics of Photon Beams

2.1.1 Photon Interactions

Photons can be considered uncharged particles that carry energy and travel at the speed of light. When they pass through a medium various interactions occur. As a result of these interactions, some or all of the photons’ energy may be transferred to the medium. Photons are considered to be indirectly ionizing radiation because they first release charged particles in the medium, which then interact through direct Coulomb interactions with orbital elections of the medium and deposit energy. Photons interact with the medium to produce charged particles through three main reactions, photoelectric effect, Compton effect and pair production(1).

2.1.1.1 Photoelectric Effect

The photoelectric effect is an interaction of a photon and a tightly bound orbital electron of the absorbing material where the photon disappears and the orbital electron is ejected from the atom. The kinetic energy ($E_K$) of the ejected electron is given as:

$$E_K = hν - E_B \quad (2-1)$$

where $hν$ is the energy of the incident photon and $E_B$ is the binding energy of the orbital electron(2). After the electron is ejected the atom is left in an ionized state. The vacancy left by the release of the orbital electron is filled by a higher shell electron resulting in the release of a characteristic x-ray or as an Auger electron(3).
The probability of the photoelectric effect is also a function of the absorbing medium and the incident photon energy. The probability of the photoelectric effect is proportional to $Z^3$, where $Z$ is the atomic number of the absorbing material. The photoelectric effect is the dominant interaction at low incident photon energies.

### 2.1.1.2 Compton Effect

An interaction between a photon and an orbital electron, which can be referred to as a ‘free’ electron, is called the Compton effect or Compton scattering. A ‘free’ electron is an orbital electron whose binding energy is much less than the energy of the incident photon $h\nu$. In the Compton effect the photon is scattered with a lower energy, $h\nu'$ and the ‘free’ electron is ejected from the atom. The kinetic energy of the recoil electron is $E_K = h\nu - h\nu'$.

The probability of Compton scattering is independent of the atomic number of the absorbing material however it is dependent on the incident photon energy. Compton scattering is the dominant interaction for photons with energies in the megavoltage range. A diagram of Compton scattering is shown in Figure 2-1.

![Diagram of the Compton Effect](image)

**FIGURE 2-1: Diagram of the Compton Effect**

### 2.1.1.3 Pair Production

Pair production is an interaction between an incident photon with energy $h\nu$, and the Coulomb field of the either the nucleus or an orbital electron of an atom in the absorbing material. The photon disappears and an electron-positron pair is created.
Because the energy of the incident photon is transformed into two particles, a threshold energy is required for the interaction to occur. If the interaction occurs in the field of the nucleus it is called nuclear pair production and the threshold energy is \( \sim 2m_e c^2 = 1.022 \) MeV. If the interaction occurs in the Coulomb field of an orbital electron it is called triplet production and has a threshold energy of \( \sim 4m_e c^2 = 2.044 \) MeV. In triplet production the photon disappears, an electron-positron pair is created and the original orbital electron is released. In both pair and triplet production, the energy of the released charged particles is equal to \( h\nu - 2m_e c^2 \).

The probability of pair production occurring is proportional to the atomic number \( Z \) of the absorbing material and the energy of the incident photon. Pair production is the dominant interactions for very high energy photons. Figure 2-2 shows the photon energy ranges where each interaction is dominant as function of the absorbing material’s atomic number, \( Z \).

![Figure 2-2: Relative predominance of the three main photon interactions with absorber atom as a function of photon energy and absorber atomic number (Z)](image)

**2.1.2 Electron Interactions**

An electron is a light, negatively charged, elementary particle that is a fundamental constituent of matter. As an electron travels through a medium, it interacts through Coulomb interactions with the atomic nuclei and orbital electrons of the absorbing material. Collisions may be elastic or inelastic. In an elastic collision, the
electron changes direction but does not lose energy. In an inelastic collision, the electron is deflected and loses energy to an orbital electron or the energy is dissipated in the form of bremsstrahlung.

Collisions between an electron and an orbital electron are characterized as either soft or hard depending on the relationship between the impact parameter, \( b \), and the atomic radius of the absorbing material, \( a \). A soft collision occurs when the incoming electron is far from the atom, i.e., if \( b \gg a \). This results in a very small amount of energy being transferred to the orbital electron. The atom becomes excited when the orbital electron is elevated to a higher energy level. Hard collisions occur when \( b \approx a \). In hard collisions, a large amount of the electron’s kinetic energy may be transferred to the orbital electron, ejecting it from the atom in a process called ionization. The ejected electron, or delta electron, has enough energy to continue on its own track depositing energy in the medium.

Electrons may also interact with the atomic nuclei of the absorbing material. This results in scattering of the electrons and energy loss in the form of x-rays or bremsstrahlung. These are referred to as radiative energy losses.

### 2.1.3 Stopping Power

Stopping power is used to describe the loss of energy of a charged particle as it moves through a medium. The linear stopping power is the expectation value of the rate of energy loss per unit path length of the charged particle as it moves through the absorbing medium. It is a function of the properties of the charged particle and of the absorbing medium. Dividing the linear stopping power by the density of the absorber is called the mass stopping power, Equation 2-2. This eliminates the dependence of the stopping power on the mass density of the absorbing material.

\[
\frac{s}{\rho} = -\frac{1}{\rho} \frac{dE}{dx} \left[ MeV \cdot cm^2 / g \right] \tag{2-2}
\]

Total stopping power (Equation 2-3) is made up of two components; collision stopping power, due to charge particle interactions with orbital electrons and radiative stopping power, due to interactions of charged particles with the nuclei of the absorbing medium.

\[
S_{tot} = S_{rad} + S_{col} \tag{2-3}
\]
Heavy and light particles experience significant energy losses due to interactions with orbital electrons however, only light charged particles suffer significant energy losses as a result of interactions with nuclei of the absorber.

### 2.1.3.1 Radiation Stopping Power

The rate of energy loss of electrons that results in the in production of Bremsstrahlung is called the mass radiation stopping power. The expression for the mass radiation stopping power is as follows:

$$ s_{rad} = \alpha Z^2 \frac{N_A}{A} \left( E_K + m_e c^2 \right) B_r $$

where,

- $c$ is the speed of light
- $\alpha$ is the fine structure constant
- $Z$ is the atomic number of the absorbing material
- $N_A$ is Avogadro’s number
- $A$ is the atomic mass number of the absorbing material
- $E_K$ is the initial kinetic energy of the charged particle
- $B_r$ is a slowly varying function of $E_K$ and $Z$

### 2.1.3.2 Collision Stopping Power

Collision stopping power can be divided into two components, soft collision stopping power and hard collision stopping power, which represents the types of collisions that result in the transfer of energy from the charged particle to the medium.

$$ \left( \frac{s_{col}}{\rho} \right) = \left( \frac{s_{col}}{\rho} \right)^{hard} + \left( \frac{s_{col}}{\rho} \right)^{soft} $$

Bethe derived an expression for the mass collision stopping power from soft collisions for heavy and light charged particles. Mass collision stopping power is a combination of Bethe theory for soft collisions with the stopping power as a result of hard collisions. For heavy charged particles the mass collision stopping power is given as:
\[
\frac{s_{col}}{\rho} = \frac{4 \pi N_A e^2 r_e^2 m_e c^2}{A} \beta^2 - z^2 \left[ \ln \left( \frac{2m_e v^2}{I} \right) - \ln \left( 1 - \beta^2 \right) - \beta^2 - \frac{c}{z} - \delta \right] \quad (2-6)
\]

where,
- \( r_e \) is the classical electron radius
- \( \beta \) is the electron or positron velocity normalized to \( c \)
- \( z \) is the atomic number of the heavy charged particle
- \( I \) is the mean ionization-excitation potential of the absorbing material
- \( C/Z \) is the shell correction
- \( \delta \) is the polarization correction

The expression for mass collision stopping power for hard collisions for light charged particles was determined by using the Møller and Bhabha differential cross sections for electrons and positrons respectively. The complete mass collision stopping power is given according to ICRU 37:

\[
s_{col} = 2 \pi m_e Z m_e c^2 \left[ \ln \left( \frac{E_K}{I} \right) + \ln \left( 1 + \frac{\tau}{2} \right) + F^+ (\tau) - \delta \right] \quad (2-7)
\]

where
- \( \tau \) is the electron or positron kinetic energy normalized to \( m_e c^2 \)
- \( F^\pm \) is the function for the kinetic energy of electrons and positrons

### 2.1.4 Absorbed Dose

Absorbed dose, Equation 2-8, or dose is defined as the mean energy imparted by ionizing radiation per unit mass \( m(4) \).

\[
D = \frac{\bar{E}}{dm} \quad (2-8)
\]

The SI unit for absorbed dose is the Gy or J/kg. Absorbed dose is the sum of all energy entering the volume of interest minus all energy being taken away by radiative processes.

### 2.1.5 Photon Percentage Depth Dose Curve

When a photon beam is incident on a phantom or patient the dose deposited varies with depth. The central axis dose distribution normalized to the dose at depth of
maximum dose \( (D_{\text{max}}) \) is referred to as the percentage depth dose (PDD). Figure 2-3 shows PDDs for photon beams of varying energies.

\[
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2_3.png}
\caption{PDD for 6 MV and 18 MV photon beams}
\end{figure}
\]

As seen in Figure 2-3, the PDD has an initial build-up region to \( D_{\text{max}} \) followed by an exponential decrease with depth after the depth of dose maximum. In the build-up region, photon interactions liberate high-energy electrons which deposit energy in the medium at some distance away from the interaction. Further photon and charged particle interactions increase electron fluence in the patient and therefore absorbed dose until \( D_{\text{max}} \). At this point charged particle equilibrium is reached where the energy transferred to charge particles and the absorbed dose are equal. Beyond \( D_{\text{max}} \) photon energy fluence decreases with depth therefore photon interactions and charged particle interactions also decrease. As a result the dose begins to decrease exponentially with increasing depth(4).

2.2 Physics of Proton Beams

2.2.1 Proton Interactions

As protons pass through a medium they interact through Coulomb interactions with atomic electrons and nuclei of the absorbing medium. Protons also experience nuclear interactions with atomic nuclei. Energetic, positively charged protons attract the orbital electrons, transfer part of their kinetic energy to the electron causing ionizations
and excitations leading to absorbed dose(4). A small amount of a proton’s kinetic energy is lost to an orbital electron during each interaction therefore each proton experiences on average 100,000s of interactions per centimeter before losing all their energy. Coulomb interactions result in smaller scattering angles than electron-electron interactions therefore protons travel in an almost direct path into the medium and have a definite range which is determined by the proton’s initial energy(5). Most scattering of proton beams is due to Coulomb interactions with atomic nuclei(4) where the heavy, positive nucleus of the absorber deflects the protons. The scattering angles are small, however a proton suffers many scattering events as it passes through a medium(5).

As with electrons, protons passing in the nuclear field of an atomic nuclei of the absorbing material can be scattered and lose energy in the form of bremsstrahlung however. The likelihood of this interaction is proportional to the inverse square of the particle mass, therefore this phenomenon is much less likely for protons than electrons because protons are much heavier than electrons(5).

Protons can collide head-on with atomic nuclei of the absorber, though rarely. Such a collision produces nuclear reactions which results in an excited nucleus and can produce secondary protons, neutrons or alpha particles(4). The nucleus is split up, and the proton loses a significant amount of energy and is deflected(5).

2.2.2 Bragg Peak

As a monoenergetic proton beam passes through a medium energy is deposited through ionizations, excitations and nuclear reactions. The rate of energy loss is not constant as the proton slows down. The entrance dose is fairly low followed by a slow increase in dose deposition with the maximum dose deposited at the end of the proton range followed by steep fall-off to zero. The rapid increase in dose deposition results in what is called a Bragg Peak. A typical depth dose distribution for a proton beam is shown in Figure 2-4.
At any point along the protons’ path, the dose deposited is governed by the mass collision stopping power for heavy charged particles (Equation 2-6). The stopping power is approximately inversely proportional to the speed, $v^2$. Therefore as the protons slow down, the mass collision stopping power increases with the maximum at the end of the proton range (4, 7).

2.2.3 Spread Out Bragg Peak

The Bragg Peak in Figure 2-2 from a monoenergetic proton beam is not practical for treating a typical tumour. In order to adequately cover the target, the Bragg peak must be spread out. This is achieved by superimposing Bragg peaks of different energies as seen in Figure 2-5. This is what is called a spread-out-Bragg-peak (SOBP). A beam of sufficient energy to cover the distal edge of the target is combined with beams of decreasing energy and intensity to uniformly cover the proximal edge of the target (4, 5).
The superposition of weighted bragg peaks of different energies results in a spread out bragg peak (SOBP) (adapted from 6)

The depth dose characteristics of protons are an advantage for proton therapy when compared to photon radiation therapy because the maximum dose can be positioned within the target for each beam angle. This results in a high dose region in the target with little dose delivered to normal tissues. A comparison of the depth dose curves for a proton beam and a photon beam normalized to the same maximum dose are shown in Figure 2-6. The regions in black illustrates where the photon beam dose exceeds the proton beam dose.
FIGURE 2-6: Percentage depth dose distribution comparison between a 16 MV photon beam and a proton SOBP with maximum proton beam energy of 200 MeV normalized to the maximum dose. Areas shaded in black indicate the advantage of proton beams over photon beams (adapted from 6).

2.2.4 Lateral Penumbra

As a proton beam travels through a medium the beam spreads out laterally. This is what is referred to as the lateral penumbra. The lateral penumbra is a function of the penetration depth. It is largest at the end of the proton range due to multiple Coulomb scattering within the patient and scattering upstream of the patient due to collimation and beam shaping devices. Typically at the end of the proton range, the lateral penumbra is a bit more than 3% of the range. A proton beam with a range of 15 cm will have a lateral penumbra of between 5 and 6 mm including the effects of scatter upstream of the patient. This is comparable to the lateral penumbra of photon beams, which is between 6 and 9 mm. High energy beams with ranges beyond 20 cm have lateral penumbra that exceed those of photon beams (5).
2.2.5 Relative Biological Effectiveness

The relative biological effectiveness (RBE) is used to describe the biological impact of the delivered dose. Protons are slightly more biologically effective than photons. Therefore, less proton dose is required to reach the same biological effect as photons. For protons, the RBE is defined as the ratio of photon dose to proton dose to reach the same biological effect. RBE is a function of the linear energy transfer (LET), the energy lost by protons per unit depth in keV/μm. LET increases slightly over the SOBP with a more pronounced increase in LET at the end of the proton range. Therefore the RBE varies within the SOBP with an increase in RBE at the end of the proton range.

ICRU 78 recommends a proton RBE of 1.1 be used. In order to aid in the comparison between photon and proton absorbed dose the RBE-weighted proton absorbed dose \(D_{RBE}\), Equation 2-9, is used. The RBE-weighted proton absorbed dose is the photon dose required to achieve the same biological effect as the proton absorbed dose, \(D\).

\[ D_{RBE} = 1.1 \times D \quad (2-9) \]

It allows for better comparison between photon and proton dose, and the selection of appropriate proton doses to achieve a specific therapeutic outcome based on previous photon therapy experience.

2.3 Treatment Beam Production and Delivery

2.3.1 Photons

2.3.1.1 Linear Accelerator

Linear accelerators (linacs) are the most common machine used in the treatment of cancer. Linacs can accelerate electrons to energies of 4 MeV to 25 MeV in straight evacuated cavities and are mounted isocentrically so that treatment can be delivered from various angles. A linac is composed of an electron gun, RF power generating system, accelerating waveguide, auxiliary system, beam transport system, beam collimation and beam monitoring. A diagram showing the components of a linac is shown in Figure 2-7.
FIGURE 2-7: Diagram of a linac(3)

The electron gun is the source of electrons. Electrons are thermionically emitted from a heated cathode, focused into a pencil beam, and enter the accelerating waveguide. The electrons are accelerated through a transfer of power from high power RF field in the accelerating waveguide that is produced in the RF power generation system by a klystron or magnetron. High-energy electrons emitted from the accelerating waveguide are bent towards the target using a beam transport system. For energies higher 6 MeV, the accelerating waveguide is positioned horizontally in the gantry therefore the electron beam must be bent 270° using bending magnets to hit the thick target in the treatment head. The auxiliary system provides vacuum pumping, water cooling and shielding required for electron acceleration.

The treatment head contains components required for photon beam production, shaping and monitoring. High-energy electrons hit a thick target where about 1% of the electron’s kinetic energy is transformed into bremsstrahlung x-rays. The photon beam is forward peaked and therefore must be flattened using a flattening filter that creates the flat distribution required for therapy. Primary and secondary collimators shape the photon beam and an ion chamber monitors the radiation output. The treatment head may
also include wedges or mulitleaf collimators (MLC) for further beam modulation and shaping. Electron beams are produced by replacing the target and flattening filter with a scattering foil.

Linacs are available in several different configurations. Some are single energy, usually 4 MV or 6MV while others produce dual energy and electron beams. The high energy linac usually provides 6 MV and 18 MV photon beams as well as electron beams of various energies(2, 3).

2.3.1.2 Helical Tomotherapy

Helical tomotherapy (HT) is an IMRT technique in which the patient is treated slice by slice in a method similar to a CT scanner. A 6 MV Linac is mounted in a CT like gantry and rotates 360 degrees. A fan beam delivers radiation as the patient is translated through a doughnut shaped aperture. The fan beam is modulated using a temporally designed multileaf collimator (MLC) consisting of a long, narrow slit with multiple leaves at right angles. The leaves move in and out of the slit to create the beam modulation while the beam is on. The Tomotherapy unit also includes an MV detector to allow MV CT scans for target localization(4). A diagram of a Tomotherapy unit is shown in Figure 2-8.
2.3.2 Protons

2.3.2.1 Accelerators

To create useful proton treatment beams, protons need to be accelerated to high energies. Cyclotrons and synchrotrons are used to accelerate proton to energies required for radiotherapy. Cyclotrons produce fixed-energy proton beams that must be modulated in order to create the SOBP required for treatment while synchrotrons produce beams with variable energies.

Cyclotrons consist of two evacuated magnets, called dees, which are separated by a small gap. An electric field created by a high voltage RF oscillator is applied across the gap. Protons are injected into the center of the cyclotron. Each time the proton crosses the gap, the polarity of the electric field is switched and the proton is accelerated across the gap. The magnetic field confines the protons to the magnet and causes them to travel in semi-circular orbits of increasing radius as they increase in energy(8). As the proton increases in speed, relativistic effects cause an increase in proton mass. The increase in
proton mass causes the time required for the protons to reach the gap to increase and become out of sync with the RF frequency. To compensate for the relativistic effects, the magnetic field in the dees is increased with increasing radius. Alternatively a synchrocyclotron can be used where the frequency of the oscillator is reduced as the proton gains energy(9). When they reach the maximum energy the proton is extracted. In order to treat most tumours at depths up to 32 cm, a cyclotron or synchrocyclotron must be able to produce beams up to 230 MeV.

A synchrotron consists of an evacuated ring in which the protons are accelerated. Protons with energies from 3 to 7 MeV are injected into the ring and accelerated in radiofrequency cavities using a sinusoidal voltage that is increased with increasing proton energy. Bending magnets are used to steer the protons around the ring. As the proton energy is increased, the magnet strength is also increased. When the beam reaches the desired energy, it is extracted. The advantage that the synchrotron has over cyclotrons is that they are able to produce all the proton beam energies required to treat tumours without the use of energy degraders(5).

FIGURE 2-9: Diagram of a cyclotron (adapted from 10)
Cyclotrons, synchrocyclotrons and synchrotrons are currently used in facilities around the world to accelerate protons for use in radiation therapy. The most commonly used accelerators are cyclotrons, supplied by either IBA (Belgium) or Varian Medical Systems (Palo Alto, CA) and synchrotrons used in systems provided by Hitachi, Ltd (Japan). Mevion Medical Systems (Littleton, MA) recently installed a superconducting synchrocyclotron in St. Louis, MO. The superconducting synchrocyclotron provides a much smaller accelerator, which is included in a single room proton therapy system.

2.3.2.2 Beam Delivery

A single accelerator is often used to provide treatment beams to several rooms. A beam transport system consisting of bending, steering and focusing magnets is used to transport the proton beam to the treatment rooms. Each treatment room is equipped with either a fixed beam line or a gantry. With a fixed beam line, the patient is usually treated in a seated position. A gantry allows the patient to be irradiated at various angles. Gantries are usually larger than in photon therapy because protons at therapeutic energies can only be bent with large radii. The gantry consists of a nozzle, containing beam monitoring, steering, shaping, and spreading devices and a telescopic snout. The snout...
allows the addition of patient-specific collimation and adjustments of the air gap between the collimator and the patient(8).

The proton beam is transported to each treatment room as a pencil beam. Two delivery methods can be used to treat the target. In the first, called passive scattering, the pencil beam is spread out to create a beam broad enough to cover the patient. The second, called spot-scanning or pencil beam scanning, magnets are used to scan the beam over the target.

2.3.2.2.1 Passive Scattering

The field sizes required for radiation therapy are typically larger than the diameter of the incoming pencil beam and therefore the beam needs to be broadened. To homogeneously cover a tumour volume, the pencil beam is broadened by placing scatterers in the beam. A double scattering system is commonly used to create the large field sizes required for radiation therapy. The first scatterer is placed near the nozzle entrance and is typically flat and made of a high Z material. A second Gaussian-shaped, bi-material high-Z and low-Z, scatterer is placed downstream. High-Z materials scatter more than low-Z materials and cause minimum energy loss. The combination of the two scattering foils results in a broad, uniform treatment beam(5, 8).

Proton therapy facilities with fixed energy beams from cyclotrons require range modulators to create the SOBP required for treatment. The SOBP is achieved through the use of range shifters and modulator wheels or ridge filters. Modulator wheels rotate in the beam and consist of segments with differing thicknesses of absorbing material. The thickness of each layer and length of time in the beam is controlled in order to create the desired SOBP. The resulting beam is a sequence of Bragg peaks with incrementally reducing ranges and weights. Ridge filters have multiple “ridges” that are shaped to produce the desired SOBP(4, 8).

Patient-specific apertures and compensators shape the treatment field to the tumour volume. Apertures are typically made of brass and are made based on projections from the treatment planning system. Compensators modulate the SOBP to the distal edge of the target. They are usually made of low-Z material and attached to the snout. Along with conforming the isodose surface to the distal edge of the PTV, range compensators
are used to compensate for irregularities in the patients’ surface and tissue heterogeneities. Figure 2-11 shows all the components required for proton radiation therapy using passive scattering(8).

**FIGURE 2-11**: Diagram showing how patient specific devices (range shifter, range modulator, aperture, and compensator) are used to shape a passively scattered proton beam to conform to the shape of the target (adapted from 6)

### 2.3.2.2 Scanning

An alternative to broad beam delivery is magnetically scanning the pencil beam and delivering Bragg peaks, called ‘spots’, throughout the target. The spots are scanned in the x-y plane perpendicular to the proton beam and the depth, z, is controlled by energy modulation. The target volume is divided into voxels and Bragg peaks are delivered to each voxel starting with the highest energy beam. Once the deepest layer is completed, the beam energy is reduced and the next layer is painted. If a cyclotron is used to accelerate the protons, an energy selection system is required to reduce the proton beam energy. The energy selection system usually consists of a degrader with variable thicknesses, often a carbon wedge, which is placed in the beam. Because distal layers deliver dose to proximal regions the intensity of subsequent layers must be reduced in
order to homogeneously treat the PTV. The scanning technique may either be static, in which the beam is turned off when the Bragg peak position is being switched, or dynamic, where the beam is continuously scanned within the target and the intensity is adjusted through the output or the speed of the scan(6, 8). A diagram illustrating pencil beam scanning is shown in Figure 2-12.

![Diagram of variable energy pencil beam scanning](adapted from 6)

**FIGURE 2-12: Diagram of variable energy pencil beam scanning (adapted from 6)**

Spot-scanning is advantageous because no patient specific apertures or compensators are required. As a result high dose regions proximal to the target do not receive high dose. Scatterers are also not required which results in fewer nuclear interactions outside the patient resulting in less neutron dose. A major advantage is the ability to use intensity modulated proton therapy (IMPT). Like IMRT, fields with inhomogeneous dose distributions are combined to create a homogeneous dose distribution in the PTV. A disadvantage of spot-scanning is that it is more sensitive to organ motion which can result in either depositing dose in normal tissue or missing part of the target(5).
2.3.2.2.3 Intensity Modulated Proton Therapy (IMPT)

During intensity modulated proton therapy, an inhomogeneous dose distribution from each field is given to the PTV. When all fields are combined, a homogeneous dose is delivered to the target. IMPT is achieved using spot-scanning. Bragg peaks are placed throughout the target and each one is considered a free variable for optimization(11). IMPT is planned using inverse planning using robust optimization techniques which can reduce the sensitivity to range and other uncertainties present in spot-scanning as well as improve dose conformity and reduce the integral dose(8).

2.4 References


Chapter 3:

Materials and Methods

In Chapter 3 the experimental method for the comparison of photon and proton plans is described. First the patient selection process is explained, followed by a description of the treatment planning process. This is followed by a description of the method used for treatment plan comparison. Finally, the risk models used for calculation of secondary cancer risk are described.

3.1 Patients

Patients used for the comparison of photon and proton therapy were selected from a group of 112 patients, 19 years of age or younger, who had appointments between June 2009 and June 2010 at Montreal General Hospital. Patients were excluded if they did not have previous treatment plans, were not treated with photon therapy, or were diagnosed with surface tumours such as keloids. Each patient was evaluated for suitability for proton radiotherapy, which was determined based on diagnosis and tumour location. Proton therapy is an accepted treatment for CNS tumours, base of skull tumours, retinoblastoma, hodgkin’s lymphoma, medulloblastoma, craniopharyngioma, ependymomas, low-grade gliomas, neuroblastoma, rhabdomyosarcomas, and low-grade astrocytomas (1, 2). It is believed that patients with tumours in locations such as the pelvis or extremities may benefit from reduced dose to normal tissue. Therefore patients were also included if it was believed that proton therapy would result in increased normal tissue sparing. From the initial 112 patients, 50 were considered suitable for proton therapy and 20 patients were re-planned using IMPT. These included 11 partial brain tumours, 1 hodgkin’s lymphoma patient, 4 patients who received craniospinal irradiation, 1 rhabdomyosarcoma of the pelvis, 1 neuroblastoma of the abdomen and 2 retinoblastomas. A summary of the patients re-planned is shown in Table 1.
### TABLE 3-1: Patient Information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Tumour</th>
<th>Treatment</th>
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<td>Brain</td>
<td>HT</td>
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<td>Brain</td>
<td>HT &amp; Cyberknife</td>
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<td>2</td>
<td>M</td>
<td>Retinoblastoma</td>
<td>Eye</td>
<td>HT</td>
</tr>
<tr>
<td>20</td>
<td>2 and 3</td>
<td>M</td>
<td>Bilateral Retinoblastoma</td>
<td>Eye</td>
<td>HT and FSRT</td>
</tr>
</tbody>
</table>

### 3.2 Treatment Planning

IMPT treatment plans were created using inverse planning in Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) with a scanning proton beam model. All proton treatment plans were created on the same CT scan as the comparable photon plan and delivered the same RBE-weighted prescription dose to the same PTV. If multiple treatment plans existed for the same patient, then a corresponding proton plan was created for each photon plan. The constraints used in inverse planning were based on those used for the photon plans. For patients treated with 3D-CRT, proton plan constraints were based on the photon radiation therapy dose volume histogram (DVH) for the target and critical structures. The patients were planned to the photon plan RBE-
weighted prescription dose in Grays using one to four beams. For each plan, the minimum number of fields required to achieve good PTV coverage were used in order to spare normal tissues. The beam arrangements were chosen based on the location of the PTV and organs and risk. Typically, beams were selected such that the beam did not pass through highly heterogeneous tissues, OAR were not directly distal to the PTV in the direction of the beam, and the air gap between the nozzle and the patient was relatively uniform over the entire field. A summary of the treatment plans is shown in Table 3-2

**TABLE 3-2: Prescription doses and fields**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prescription dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th># fractions</th>
<th>Fields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>52.2</td>
<td>1.8</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>50.4</td>
<td>1.8</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>50.4</td>
<td>1.8</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>46.8</td>
<td>1.8</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>50.4</td>
<td>1.8</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>1.8</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>55.8</td>
<td>1.8</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>50.4</td>
<td>1.8</td>
<td>28</td>
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<tr>
<td></td>
<td>50.4</td>
<td>1.8</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>21</td>
<td>1.5</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>21.6</td>
<td>1.8</td>
<td>12</td>
<td>2</td>
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<tr>
<td>15</td>
<td>23.4</td>
<td>1.8</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>36</td>
<td>1.8</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>36</td>
<td>1.8</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>1.8</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>45</td>
<td>1.8</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>45</td>
<td>1.8</td>
<td>25</td>
<td>1</td>
</tr>
</tbody>
</table>
During the planning process, proton plans were compared to the patients’ photon treatment plan in order to achieve the similar target coverage and adequate sparing of organs at risk. Comparing the dose distribution in the 3D volume of the patient as well as comparing the DVH accomplished this. Helical tomotherapy (HT) dose distributions were imported into Eclipse for accurate plan comparisons. Proton therapy plans were normalized to match the percent volume of the PTV covered by the prescription dose in the photon plans. When an acceptable IMPT plan was obtained a more in-depth plan comparison was performed.

3.3 Treatment Plan Comparison

Photon and proton plans were compared for target coverage, normal tissue dose and integral dose. Plan comparison DVHs were used to compare target coverage and dose to OARs. Metrics used for further comparison of the target volume were conformity index, homogeneity index, near maximum dose, near minimum dose and median dose. The minimum dose received by the hottest 2% of the volume or the near-maximum dose (D2%), the minimum dose received by 98% of the PTV or the near-minimum dose (D98%) and the dose received by 50% of the PTV or medium dose (D50%) were obtained from the DVH for the PTV for photon and proton plans(3). Conformity indices for the 95% and 100% isodose lines further compared target coverage where values close to one are indicative of a conformal plan. Target homogeneity or uniformity was calculated for proton and photon plans based on the volumes of the PTV and volumes enclosed by the 95% or 100% isodose lines. Normal tissue sparing achieved using proton therapy was compared by determining the volume of the body receiving 2 Gy (V2Gy) and 5 Gy (V5Gy) as well as the integral dose. The body volume was defined as the extent of the body included in the CT scan.

3.3.1 Conformity Index

The conformity index (CI) is an indicator of the quality of the dose distribution. It characterizes the degree to which the high dose region conforms to the PTV. It is defined as the treated volume divided by the volume of the PTV(4). In this study the conformity index was calculated for two different treated volumes, the volume receiving 95% of the
prescribed dose ($CI_{95\%}$), Equation 3-1, and the volume receiving 100% of the prescribed dose $CI_{100\%}$ Equation 3-2.

\[
CI_{95\%} = \frac{\text{Volume receiving 95\% of the prescribed dose}}{\text{Volume of the PTV}} \quad (3-1)
\]

\[
CI_{100\%} = \frac{\text{Volume receiving 100\% of the prescribed dose}}{\text{Volume of the PTV}} \quad (3-2)
\]

A conformity index of 1 corresponds to perfect conformity. If the conformity index is larger than 1 that indicates that the irradiated volume is larger than the PTV and values lower than 1 indicate that part of the PTV is not completely irradiated to the desired dose level. In general a CI between 1 and 2 are acceptable, values between 0.9 and 1, or 2 and 2.5 are considered minor violations and values less than 0.9 and greater than 2.5 are major violations(5).

### 3.3.2 Homogeneity Index

The homogeneity index (HI) is also an indicator of the quality of the dose distribution in the PTV. It describes the degree of dose uniformity within the target volume and is calculated according to Equation 3-3.

\[
HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (3-3)
\]

The smaller the homogeneity index the more uniform the dose distribution within the target(3).

### 3.3.3 Integral Dose

Integral dose is another method used to compare proton and photon dose distributions. It is a measure of the total energy absorbed in the body from all treatment beams and is the product of the absorbed dose and mass of the irradiated volume. In this study, the integral dose was calculated from the differential dose volume histogram for the body. The differential dose volume histogram is a plot of the volume of a specified structure that receives an absorbed dose, $D$, within an interval $\Delta D$. The integral dose in joules was calculated according to Equation 3-4.

\[
\text{integral dose} = \frac{0.1 \rho \sum (D \times V)}{1000} \quad (3-4)
\]
where,
\[ D \] is the center dose of each dose bin in Gy
\[ V \] is the volume of the body irradiated in each dose bin in cm\(^3\)/Gy
\[ 0.1 \] is the dose bin size in Gy or J/kg
\[ \rho \] is the density of tissue, assumed to be equivalent to water \( \sim 1 \) g/cm\(^3\)
\[ 1000 \] kg to g conversion factor

### 3.4 Modeling Risk of Secondary Cancer

Most risk models for secondary cancer are derived from dose response relationships based on atomic bomb survivor data. However there is considerable uncertainty in the risk models because atomic bomb survivors experience a single, acute radiation exposure, while radiation therapy patients typically receive fractionated radiation doses. Between 0.1 and 2.5 Gy the dose-response relationship for radiation induced cancer is a linear relationship. However outside this range there is uncertainty in the dose-response relationships\(^6\). Most risk models assume a linear dose-response relationship and are therefore only valid in the low-dose region. These models are valid for workers exposed to low dose radiation and use whole body effective dose calculated using radiation and organ weighting factors which are gender and age averaged. These models specify that they are not to be used for single patients or site specific tumours\(^7\). Despite this, many studies have used these models to predict the risk of secondary cancer following radiation therapy, where doses are much higher than 2.5 Gy.

In this study, two methods were used to determine the risk of secondary cancer. The first relates the relative risk of secondary cancer to the integral dose. The second applies the concept of organ equivalent dose (OED) to the DVH and then determine the excess absolute risk and cumulative risk of secondary cancer as described by Schneider et al\(^8\).

#### 3.4.1 Integral dose risk model

The relative risk (RR) of secondary cancer, defined as the incidence of disease in an exposed population divided by the incidence of disease in an unexposed population, was calculated based on integral dose using a linear model derived from data obtained
from Nguyen et al.(9). Nguyen et al. found a significant linear dose-response relationship between the risk of secondary malignancy and integral dose in a study of 4401 three-year survivors of childhood cancer treated between 1947 and 1986 in Great Britain and France. The results presented by Nguyen et al. were plotted and fitted to a linear function shown in Figure 3-1.

![Figure 3-1](image.png)

**FIGURE 3-1**: Plot relating integral dose with the relative risk of secondary malignancy in survivors of childhood cancer. The blue line represents results presented by Nguyen et al. and the red line is the linear fit.

The relative risk of secondary cancer was calculated for all patient plans according to Equation 3-5.

\[
RR = (0.01664 \times \text{integral dose}) + 1
\]  

(3-5)

### 3.4.2 Organ Equivalent Dose Model

For any dose distribution, the organ equivalent dose (OED) is a calculation of dose based on different radiobiological parameters described below. The OED is the same if it causes the same radiation induced cancer rate for a given organ(10). The OED is based on the knowledge of the dose-response relationship for secondary cancers, which is linear at low doses and non-linear or linear at high doses. The dose-response
relationship at high doses may be linear, fall off exponentially due to cell killing or level off. The OED for the body contour was calculated from the DVH assuming three different dose-response curves; linear (Equation 3-6), linear-exponential (Equation 3-7), and plateau (Equation 3-8).

\[
OED = \frac{1}{V} \sum_i V_i D_i \tag{3-6}
\]

\[
OED = \frac{1}{V} \sum_i V_i D_i \exp(-\alpha D_i) \tag{3-7}
\]

\[
OED = \frac{1}{V} \sum_i V_i \left(1 - \frac{\exp(-\delta D_i)}{\delta}\right) \tag{3-8}
\]

where,

\( V \)

is the total body volume

\( V_i \)

is the volume in each dose bin

\( D_i \)

is the dose in each dose bin

\( \alpha \)

is an organ specific cell sterilization parameter

\( \delta \)

is an organ specific model parameter

The OED is a dose-response weighted dose variable that is proportional to the cancer risk rate for a particular population and can be scaled to determine the excess absolute risk (EAR) of secondary cancer in different populations. The EAR is defined as the rate of disease in an exposed population minus the rate of disease in an unexposed population and was calculated according to Equation 3-9.

\[
\text{EAR}(D, e, a, s) = \beta OED \exp\left(\gamma_e (e - 37) + \gamma_a \ln\left(\frac{a}{46}\right)\right)(1 \pm s) \tag{3-9}
\]

where,

\( \beta \)

is the model initial slope

\( \gamma_e \)

is an age at exposure parameter

\( e \)

is the age at exposure

\( \gamma_a \)

is an attained age parameter

\( a \)

is the attained age

\( s \)

is gender parameter (+ for females, − for males)
The model parameters were determined from a combined fit from Japanese atomic bomb survivor data and Hodgkin’s lymphoma patient data. The parameters used were taken from Schneider et al. and are listed in Table 3-3.

**TABLE 3-3: OED model parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>0.1704</td>
</tr>
<tr>
<td>$\gamma_e$</td>
<td>-0.0277</td>
</tr>
<tr>
<td>$\gamma_a$</td>
<td>2.409</td>
</tr>
<tr>
<td>Linear exponential model $\beta$</td>
<td>10.774</td>
</tr>
<tr>
<td>Linear exponential model $\alpha$</td>
<td>0.044</td>
</tr>
<tr>
<td>Plateau model $\beta$</td>
<td>11.677</td>
</tr>
<tr>
<td>Plateau model $\delta$</td>
<td>0.139</td>
</tr>
<tr>
<td>Linear model $\beta$</td>
<td>4.184</td>
</tr>
</tbody>
</table>

The cumulative risk of secondary cancer, defined as the probability that a patient who was treated at age $e$ will develop a secondary cancer within their lifetime, was estimated by equation 3-10, assuming a life expectancy 80 years.

$$C(a) = \sum_{e=1}^{a} \left\{ \text{EAR}(D, e, a, s) \frac{S(a)}{S(e)} \right\}$$

(3-10)

The cumulative risk estimate takes into account the survival function, where $S(a)$ (Equation 3-11) is the probability at birth that a person will reach age $a$. $S(a)/S(e)$ is a conditional probability function taken from Kellerer et al. that describes the probability that a person alive at age $e$ will live to at least age $a$.

$$S(a) = \exp(-c_1 \exp(c_2 a))$$

(3-11)

Where $c_1=0.0015$ and $c_2=0.0820$ for males and $c_1=0.005$ and $c_2=0.0905$ for females.

The OED model was applied to each photon and proton in a MATLAB®, version 7.11 (R2010b), (MathWorks®, Natick, MA) function created to calculate the OED, EAR,
and cumulative risk from the differential DVH. Each plan, including the CT, dose and DVH, were exported from Eclipse in DICOM-RT format and converted to a matlab format using a software package developed at the University of Washington in St Louis called Computational Environment for Radiation Research (CERR), version 3.3 Beta 1. CERR is written in the Matlab language and allows treatment plans to be imported from a DICOM-RT format, saved in Matlab and displayed. A Matlab function was created to calculate the OED, EAR and cumulative risk of secondary cancer using the treatment plan in Matlab format, CERR functions and the date of the first radiotherapy treatment.

3.5 References


Chapter 4:

Results

In this chapter the results are presented. The first section presents a comparison of the photon and IMPT plans in terms of target coverage, dose to organs at risk, body contour dose and the integral dose. Treatment plan comparisons are presented according to site of irradiation or disease. The second section presents the relative risk of secondary cancer calculated according to the integral dose model (1). Finally, secondary cancer risks calculated according to the OED model (2) are presented according to site of irradiation or disease.

4.1 Treatment Plan Comparison

All IMPT plans were planned such that the volume of the PTV receiving 100% of the prescription dose ($V_{100\%}$) was matched to the photon plan.

4.1.1 Partial Brain Irradiation

4.1.1.1 Target Coverage

For all plans, the volume receiving the prescription dose was matched in the photon and proton plans. A typical partial brain irradiation dose distribution for Tomotherapy based IMRT (HT) is shown in Figure 4-1a and for IMPT in Figure 4-1b. The IMPT distribution shows a hotspot outside the target volume as a result of the field overlap. The PTV coverage for this patient was similar for both the HT and IMPT plans as shown in the dose volume histogram (DVH) in Figure 4-2a with the IMPT plan having a CI$_{95\%}$ of 1.40 versus 1.64 for the HT plan. The CI$_{100\%}$ was 0.98 and 1.28 for the IMPT and HT plans respectively. The HT had the highest HI of 0.04 compared to 0.02 for the IMPT plan. Acceptable values for the CI lie between 1 and 2 with the most conformal plan having a CI of 1. A HI of zero indicates an almost homogeneous dose distribution.

The target coverage for proton and photon plans was similar for all brain patients and produced similar CI$_{95\%}$, CI$_{100\%}$ and HI values. A target coverage comparison for all patients treated with partial brain irradiation is shown in Table 4-1.
**TABLE 4-1: Comparison of 95% and 100% conformity indices and homogeneity index for partial brain irradiation patient treatment plans**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>CI$_{95%}$</th>
<th>CI$_{100%}$</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HT</td>
<td>1.51</td>
<td>1.09</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.52</td>
<td>1.08</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>HT</td>
<td>1.52</td>
<td>1.06</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.56</td>
<td>1.02</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>HT</td>
<td>1.29</td>
<td>1.03</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.46</td>
<td>1.10</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>HT</td>
<td>1.42</td>
<td>0.94</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.56</td>
<td>1.00</td>
<td>0.04</td>
</tr>
<tr>
<td>5</td>
<td>IMRT plan 1</td>
<td>1.46</td>
<td>1.15</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>IMRT plan 2</td>
<td>1.35</td>
<td>1.14</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>IMRT plan 2</td>
<td>1.47</td>
<td>1.27</td>
<td>0.05</td>
</tr>
<tr>
<td>6</td>
<td>IMRT plan 1</td>
<td>1.56</td>
<td>1.12</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IMRT plan 2</td>
<td>1.42</td>
<td>1.13</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IMRT plan 2</td>
<td>1.45</td>
<td>1.17</td>
<td>0.03</td>
</tr>
<tr>
<td>7</td>
<td>3D-CRT</td>
<td>1.55</td>
<td>0.99</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>1.15</td>
<td>0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>8</td>
<td>IMRT</td>
<td>1.28</td>
<td>0.92</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>1.32</td>
<td>0.93</td>
<td>0.07</td>
</tr>
<tr>
<td>9</td>
<td>HT</td>
<td>1.62</td>
<td>1.28</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.40</td>
<td>0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>10</td>
<td>IMRT</td>
<td>1.17</td>
<td>1.00</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.23</td>
<td>1.02</td>
<td>0.02</td>
</tr>
<tr>
<td>11</td>
<td>HT</td>
<td>1.35</td>
<td>1.03</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>1.38</td>
<td>1.05</td>
<td>0.04</td>
</tr>
</tbody>
</table>
4.1.1.2 Organs at Risk

The dose to critical structures in the brain varied among plans depending on the location of the PTV within the brain. In proton plans, organs at risk outside the field and
distant from the PTV showed a reduction in dose compared to photon techniques while those adjacent to the PTV had similar dose distributions in photon and IMPT plans. IMPT plans were able to match or better the photon DVH levels for many structures in the brain particularly in the low dose regions. Table 4-2 shows a comparison for a few OAR in the brain for all partial brain patients. In the brainstem the $V_{10Gy}$ was reduced in IMPT plans for all patients except patients 3 and 4, where the $V_{10Gy}$ was the same. However, the maximum doses in the brainstem were similar for all patients in IMPT and photon plans. $V_{5Gy}$ and $D_{max}$ in the right and left optic nerves were lower in the IMPT plans compared to the photon plans with the exception of the right optic nerve in patient 11 where $D_{max}$ (55 Gy) and $V_{5Gy}$ (100%) in both IMPT and HT plans were similar. For the chiasm, $V_{20Gy}$ was lower in IMPT plans compared to photon plans with the exception of patients 9, 10 and 11 where the values were similar. $D_{max}$ in the chiasm was the same or lower in all IMPT plans compared to photon plans except for patient 10 where the $D_{max}$ was 6 Gy and 22 Gy in the IMRT and IMPT plans respectively. Similarly the right cochlea had similar or lower values for $V_{20Gy}$ and $D_{max}$ in IMPT plans compared to photon plans. The right cochlea in patient 10 had a higher $V_{20Gy}$ (7%) in the IMPT plan compared to 0% in the IMRT plan, however the mean dose to the right cochlea was the same in both plans. A typical plan comparison DVH showing the dose sparing in OARs achieved by IMPT is shown in Figure 4-2b. For this patient, protons offer a reduction in the DVH for the left optic nerve, brainstem and left cochlea.
TABLE 4-2: Photon and IMPT OAR DVH plan comparison for all partial brain patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>Brainstem</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
<th>0 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Volume, Mean or Max Dose (Gy)</td>
<td>V10Gy</td>
<td>Dmax</td>
<td>V5Gy</td>
<td>Dmax</td>
<td>V20Gy</td>
<td>Dmax</td>
<td>V20Gy</td>
<td>Dmean</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>HT</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>19</td>
<td>100</td>
<td>17</td>
<td>78</td>
<td>45</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
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<td>-</td>
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<td>2</td>
<td>0</td>
<td>4</td>
<td>67</td>
<td>43</td>
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<td>-</td>
</tr>
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<td>-</td>
<td>-</td>
<td>100</td>
<td>9</td>
<td>100</td>
<td>10</td>
<td>0</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
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<td>IMPT</td>
<td>91</td>
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<tr>
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<td>55</td>
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<td>55</td>
<td>100</td>
<td>56</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>
4.1.1.3 Body Volume

For all patients, IMPT plans showed a reduction in the body volume receiving low doses as shown in the Figure 4-2b. The percentage of the contoured body volume receiving at least 2 Gy ($V_{2\text{Gy}}$) and at least 5 Gy ($V_{5\text{Gy}}$) for the IMPT and HT plans is shown in Figure 4-3 and 4-4 respectively. The volume receiving at least 2 Gy and at least 5 Gy was higher for all photon plans. The average difference of the $V_{2\text{Gy}}$ and $V_{5\text{Gy}}$ between the photon and IMPT plans was 71 ± 14% and 70 ± 14% respectively.

![Figure 4-3: Comparison of the contoured body volume receiving at least 2 Gy (red, photon; blue, IMPT)](image_url)
4.1.1.4 Integral Dose

For all brain patients, the integral dose was higher in all photon plans. A comparison of the integral dose for each patient plan is shown in Figure 4-5. IMPT plans showed a significant reduction in integral dose compared to the photon plans with an average percent difference between the photon and proton plans of 12 ± 2%.

FIGURE 4-4: Comparison of the contoured body volume receiving at least 5 Gy (red, photon; blue, IMPT)
FIGURE 4-5: Integral dose comparison done by patient plan (red, photon; blue, IMPT)

4.1.2 Retinoblastoma

The dose distributions for a patient who was treated for retinoblastoma to a small target within the eye is shown in Figure 4-6 and for a patient treated with whole globe irradiation is shown in Figure 4-7.

FIGURE 4-6: Dose distribution for patient 19. a) HT Plan b) IMPT plan (isodose colour wash: red, 45 Gy; yellow, 40 Gy; green, 25 Gy; cyan, 15 Gy; blue, 5 Gy)
CHAPTER 4

Results

FIGURE 4-7: Dose distributions for patient 20. a) Fractionated stereotactic radiation therapy plan (FSRT) b) IMPT plan2 (isodose colour wash: red, 45 Gy; yellow, 40 Gy; green 25 Gy; cyan, 15 Gy; blue, 5 Gy)

4.1.2.1 Target

The volume of the PTV receiving at least 45 Gy ($V_{45Gy}$) was matched in the photon and proton plans. A comparison of the PTV coverage for the retinoblastoma patients is shown for the Figure 4-8a, 4-9a and Table 4-3.

TABLE 4-3: Comparison of 95% and 100% conformity indices and homogeneity index for retinoblastoma patient treatment plans. (FRST=fractionated stereotactic radiation therapy)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>CI$_{95%}$</th>
<th>CI$_{100%}$</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>HT</td>
<td>1.90</td>
<td>1.39</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>2.89</td>
<td>1.74</td>
<td>0.08</td>
</tr>
<tr>
<td>20</td>
<td>HT</td>
<td>2.33</td>
<td>1.53</td>
<td>0.03</td>
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<tr>
<td></td>
<td>IMPT plan 1</td>
<td>4.31</td>
<td>2.47</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>FSRT plan</td>
<td>1.12</td>
<td>0.90</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>IMPT plan 2</td>
<td>1.23</td>
<td>0.91</td>
<td>0.10</td>
</tr>
</tbody>
</table>
The CI$_{95\%}$ and CI$_{100\%}$ were significantly higher in the proton plans however the difference between these values in the FSRT and IMPT plan is significantly lower than between the HT and IMPT plans. The homogeneity indices were higher in the IMPT plans compared to the photon plans.

4.1.2.2 Organs at Risk

The comparison DVH for small target irradiation and whole globe irradiation is shown in Figure 4-8 and 4-9 respectively. A summary of the DVH dose levels for the contoured body, organs at risk and the integral dose for all retinoblastoma patient plans is shown in Table 4-4.

\textbf{FIGURE 4-8: Patient 19 DVH plan comparison (Solid lines, HT plan; dashed lines, IMPT plan) a) Target and contoured body DVH (red, PTV; green, body) b) OAR DVH (magenta, left optic nerve; orange, right eye; black, left lens; and blue, orbital bone)
FIGURE 4-9: Patient 20 DVH plan comparison for whole globe irradiation (Solid lines, FSRT plan; dashed lines, IMPT plan) a) Target and contoured body DVH (red, PTV; green, body) b) OAR DVH (magenta, right optic nerve; orange, right lens; and blue, orbital bone)

TABLE 4-4: Photon and IMPT OAR DVH plan comparison

<table>
<thead>
<tr>
<th>Structure, DVH dose level</th>
<th>% Volume, Mean or Max Dose (Gy), or Integral dose (J) for each patient and technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>HT</td>
</tr>
<tr>
<td>Body</td>
<td></td>
</tr>
<tr>
<td>$V_{2Gy}$</td>
<td>18</td>
</tr>
<tr>
<td>$V_{5Gy}$</td>
<td>7</td>
</tr>
<tr>
<td>Integral Dose</td>
<td>2.0</td>
</tr>
<tr>
<td>Orbital Bone</td>
<td></td>
</tr>
<tr>
<td>$V_{20Gy}$</td>
<td>20</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td></td>
</tr>
<tr>
<td>Max Dose</td>
<td>48</td>
</tr>
<tr>
<td>Lens</td>
<td></td>
</tr>
<tr>
<td>Max Dose</td>
<td>8</td>
</tr>
</tbody>
</table>
The DVH for the IMPT plan is worse or the same as the photon plan DVH for many structures. In particular, the $V_{20Gy}$ to the orbital bone, which is a known threshold for abnormal bone growth, is higher in the IMPT plan compared to the HT plan for patient 19. The lens and optic nerve had differences in the DVH however these structures were under the tolerance doses in both photon and proton plans. Significant dose sparing was observed in patient 19 in the contra-lateral eye (R eye) which received no dose in the IMPT plan compared to a maximum dose of 8 Gy in the HT plan.

### 4.1.3 Hodgkin’s Lymphoma

The HT dose distribution for a Hodgkin’s Lymphoma patient is shown in Figure 4-10a and the IMPT dose distribution is shown in Figure 4-10b.

**FIGURE 4-10: Dose distribution for patient 13 a)HT plan b)IMPT plan (isodose colourwash: red, 21 Gy; yellow, 17.5 Gy; green, 12.5 Gy; cyan, 7.5 Gy; blue, 2.5 Gy)**

#### 4.1.3.1 Target

The volume receiving the prescription dose was matched in the HT and IMPT plans. The dose distributions show good target coverage in both the HT and IMPT plans, as shown in Figure 4-11a, with the IMPT plan having a $CI_{95\%}$ of 1.39 versus the 1.42 for the HT plan. The $CI_{100\%}$ was 1.09 for the HT plan and 1.18 for the IMPT plan. The HI for the HT and IMPT plans was 0.07 and 0.06 respectively.
4.1.3.2 Organs at Risk

The lung, spinal cord and heart have a smaller volume receiving a low radiation in the IMPT plan compared to the HT plan. Figure 4-11b shows the plan comparison DVH for the heart and spinal cord and Table 4-5 gives a summary of the plan comparison DVH for this patient.

TABLE 4-5: Patient 13, IMRT and IMPT OAR DVH plan comparison

<table>
<thead>
<tr>
<th>Structure, DVH dose level</th>
<th>HT</th>
<th>IMPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Volume, Mean or Max Dose (Gy) or Integral dose (J) for each technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{2\text{Gy}}$</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>$V_{5\text{Gy}}$</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Integral dose</td>
<td>52.9</td>
<td>36.4</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{5\text{Gy}}$</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10\text{Gy}}$</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>$V_{20\text{Gy}}$</td>
<td>17</td>
<td>16</td>
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<tr>
<td>Mean Dose</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>
The $V_{20Gy}$ in lung, a threshold for the development of radiation induced pneumonitis, and the mean lung dose was similar in HT and IMPT plans. The $V_{18Gy}$ in the heart was the same for HT and IMPT plans. Below 18 Gy, the DVH for the heart is lower in the proton plan compared to the HT plan however above 18 Gy the IMPT show a slight increase in the percentage volume receiving high radiation dose. The biggest difference between the photon and proton plans is the dose received by the spinal cord where the percentage of the volume receiving dose is reduced for IMPT compared to HT. The IMPT plan has a slightly higher maximum dose to the spinal cord than the HT plan however, a dose of 22 Gy to the spinal cord is much less than the $D_{max}$ of 50 Gy which is associated with a 0.2% rate of radiation induced myelopathy(3).

### 4.1.3.3 Body and Integral Dose

The body $V_{2Gy}$ and $V_{5Gy}$ is slightly reduced in the IMPT plans compared to the HT plans, as shown in Table 4-3. While protons offer a reduction in the $V_{2Gy}$ and $V_{5Gy}$, the reduction is not as large as in some other areas of the body. However, the integral dose in the body is reduced from 59.2 J for HT to 36.4 J for IMPT.
4.1.4 Abdominal Irradiation

The HT dose distribution for a patient treated for a neuroblastoma in the abdomen is shown in Figure 4-12a and the IMPT distribution is shown in Figure 4-12b.

\[ \text{FIGURE 4-12: Dose distributions for patient 14. a)HT plan b)IMPT plan (isodose colourwash: red, 21.6 Gy; yellow, 17.5 Gy; green, 12.5 Gy; cyan, 7.5 Gy; blue, 2.5 Gy)} \]

4.1.4.1 Target

The PTV volume receiving 100% of the prescribed dose ($V_{100\%}$) was matched in the photon and proton plans. A DVH plan comparison for the target, shown in Figure 4-13a, shows equal target coverage however with a CI$_{95\%}$ of 1.29 for the HT plan and 1.70 for the IMPT plan. The CI$_{100\%}$ was 0.98 and 1.10 for the HT and IMPT plans respectively. The HT and IMPT plans had an identical HI of 0.04.

4.1.4.2 Organs at Risk

While photon and proton plans have similar target coverage there are significant differences in the DVH for the contoured body, shown in Figure 4-13a, and the organs at risk, Figure 4-13b and Table 4-6. The liver shows smaller percentage volume receiving low doses in the IMPT plan compared to the HT plan. The left kidney receives more dose in the IMPT while the spinal cord receives similar doses in both plans.
FIGURE 4-13: Patient 14 DVH plan comparison (Solid lines, HT plan; dashed lines, IMPT plan) a) Target and contoured body DVH (red, PTV; green, body) b) OAR DVH (magenta, spinal cord; green, liver; and blue, left kidney)

TABLE 4-6: Patient 14, IMRT and IMPT OAR DVH plan comparison

<table>
<thead>
<tr>
<th>Structure, DVH dose level</th>
<th>% Volume, Mean or Max Dose (Gy), or Integral dose (J) for each technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HT</td>
</tr>
<tr>
<td>Body</td>
<td></td>
</tr>
<tr>
<td>( V_{2GY} )</td>
<td>40</td>
</tr>
<tr>
<td>( V_{5GY} )</td>
<td>28</td>
</tr>
<tr>
<td>Integral dose</td>
<td>24.5</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Mean Dose</td>
<td>6</td>
</tr>
<tr>
<td>L Kidney</td>
<td></td>
</tr>
<tr>
<td>( V_{12GY} )</td>
<td>56</td>
</tr>
<tr>
<td>( V_{20GY} )</td>
<td>26</td>
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<tr>
<td>Mean Dose</td>
<td>14</td>
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<tr>
<td>Spinal Cord</td>
<td></td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>19</td>
</tr>
</tbody>
</table>
The percentage of the liver receiving doses less than ~12 Gy is smaller in the IMPT plan which results in a mean dose of 2 Gy compared to 6 Gy for the IMRT plan. For the left kidney, the IMPT plan delivers dose to a larger percentage volume up to about 22 Gy compared to the HT plan. The two proton fields used in the plan pass through the left kidney which results in a higher dose to the organ compared to HT which through the combination of a 360° fan beam minimizes the dose to the left kidney. The increase in dose to the left kidney is not considered a problem because the kidney is a parallel organ. When assessing the risk of renal dysfunction, the mean dose to both kidneys is considered.

The spinal cord has a similar DVH for most dose levels with the IMPT delivering a slightly higher percentage of the volume receiving above 15 Gy than the HT plan. The proton plan delivers more radiation dose to the spinal cord because the posterior proton field passes directly through the spinal cord. In the IMPT plan, the dose to the spinal cord could have been reduced by avoiding a posterior field however other beam angles such as an anterior field would have passed through the lungs and stomach, both of which contain air. The differences in density between tissue and air would have resulted in larger uncertainties in the proton beam range resulting in the delivering high dose to normal tissue or under dosing the target. However, a dose of 21 Gy to the spinal cord is much less than the tolerance dose of 50 Gy that is associated with a 0.2% rate of radiation induced myelopathy.

4.1.4.3 Body and Integral Dose

The body $V_{2\text{Gy}}$ and $V_{5\text{Gy}}$ was reduced in the IMPT plans compared to the HT plans, as shown in Table 4-6. The integral dose for the body is also lower for the IMPT plan at 16.5 J compared to 24.5 J for the HT plan. HT has been shown to achieve a conformal dose distribution at the price of larger volumes receiving low dose, therefore it is not unexpected to see the differences in the integral dose and the DVH for the body contour between the IMPT and HT.
4.1.5 Pelvic Irradiation

The HT dose distribution for a patient treated for rhabdomyosarcoma of the pelvis is shown in Figure 4-14a and the IMPT dose distribution is shown in Figure 4-14b.

![Image](image1.png)

*FIGURE 4-14: Plan 1 dose distributions for patient 12. a) HT plan b) IMPT plan (isodose colourwash: red, 50 Gy; yellow, 40 Gy; green, 30 Gy; cyan, 15 Gy; blue, 5.5 Gy)*

4.1.5.1 Target

Both distributions show good target coverage, Figure 4-15a, with CI\(_{95}\) of 1.25 and 1.27 for the HT and IMPT plans respectively. The CI\(_{100}\) was also similar at 1.04 and 1.03 for the HT and IMPT plans respectively. The homogeneity index in the target was 0.05 for the IMRT plan and 0.04 for the IMPT plan.

The second plan also had good target coverage for both HT and IMPT plans with a lower CI\(_{95}\) of 1.31 for the IMPT plan compared to 1.42 for the HT plan. The CI\(_{100}\) was 0.94 and 0.92 for the HT and IMPT respectively. HT plan2 had a lower HI of 0.02 compared to 0.05 for the IMPT plan.

4.1.5.2 Organs at Risk

The bladder, rectum and spinal cord have smaller volume receiving a low dose radiation in the IMPT plan compared to the HT plan as shown in Figure 4-15 and Table 4-7.
FIGURE 4-15: Patient 12 plan 1 DVH plan comparison (Solid lines, HT plan; dashed lines, IMPT plan) a) Target and contoured body DVH (red, PTV; green, body) b) OAR DVH (magenta, rectum; black, bladder; and blue, spinal cord)

In plan 1, DVH for the IMPT plan is lower than the HT plan until a dose of 45 Gy and 34 Gy for the bladder and rectum respectively. The spinal cord in the HT receives a small dose however the proton plan does not deliver any dose to the spinal cord. The second plan shows similar DVH trends as shown for plan 1 with decreased volumes of the OARs receiving low radiation doses and larger volumes receiving higher doses in the IMPT plan.
TABLE 4-7: Patient 12, HT and IMPT Body DVH plan comparison

<table>
<thead>
<tr>
<th>Structure, DVH dose level</th>
<th>HT plan 1</th>
<th>IMPT plan 1</th>
<th>HT plan 2</th>
<th>IMPT plan 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{2Gy}$</td>
<td>41</td>
<td>17</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>$V_{5Gy}$</td>
<td>36</td>
<td>15</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Integral dose</td>
<td>66.1</td>
<td>37.0</td>
<td>51.3</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10Gy}$</td>
<td>100</td>
<td>63</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>$V_{20Gy}$</td>
<td>90</td>
<td>53</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>$V_{45Gy}$</td>
<td>30</td>
<td>30</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{10Gy}$</td>
<td>100</td>
<td>51</td>
<td>89</td>
<td>58</td>
</tr>
<tr>
<td>$V_{20Gy}$</td>
<td>79</td>
<td>37</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>$V_{34Gy}$</td>
<td>24</td>
<td>24</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>3</td>
<td>0</td>
<td>1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

4.1.5.3 Body and Integral Dose
The body $V_{2Gy}$ and $V_{5Gy}$ was reduced in the IMPT plans compared to the HT plans, as shown in Table 4-7. The integral dose for the body was also lower for the IMPT plans compared to the HT plans.
4.1.6 Craniospinal Irradiation

For all plans, the volume receiving the prescription dose was matched in the photon and proton plans. A typical HT and an IMPT dose distribution for a patient who received craniospinal irradiation (CSI) are shown in Figure 4-16.

![Figure 4-16: A Typical CSI dose distributions (patient 18). a) HT plan b) IMPT](image)

(isodose colourwash: red, 36 Gy; orange, 32.5 Gy; yellow, 30 Gy; green, 22.5 Gy; cyan, 12.5 Gy; blue, 5 Gy)

4.1.6.1 Target

The PTV coverage for this patient was similar for both the HT and IMPT plans as shown in the dose volume histogram (DVH) in Figure 4-17a with the IMPT plan having a CI$_{95\%}$ of 1.35 compared to 1.52 for the HT plan. The CI$_{100\%}$ was 1.33 and 1.18 for the IMPT and HT plans respectively. The HT had the highest HI of 0.04 compared to 0.03 for the HT plan. The target coverage for proton and photon plans was similar for all CSI patients and produced similar CI$_{95\%}$, CI$_{100\%}$ and HI values.
4.1.6.2 Organs at Risk

The IMPT showed significant dose reduction in the heart, lungs, esophagus and kidneys compared to HT with the heart and kidneys receiving little or no dose with IMPT while the dose to the esophagus and lungs was greatly reduced as illustrated in the DVH in Figure 4-17b. Table 4-8 gives a summary of the DVH for critical structures for all CSI patients.

FIGURE 4-17: DVH comparison for patient 18 (Solid lines, HT plan; dashed lines, IMPT plan) a) Target and contoured body DVH (red, PTV; green, body) b) OAR DVH (magenta, heart; black, kidneys; orange, lungs; and blue, esophagus)
### TABLE 4-8: IMRT and IMPT OAR DVH plan comparison for all CSI patients

<table>
<thead>
<tr>
<th>Structure, DVH dose level</th>
<th>% Volume, Mean Dose (Gy), Integral dose (J) for each patient and technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
</tr>
<tr>
<td>Body</td>
<td></td>
</tr>
<tr>
<td>$V_{2 Gy}$</td>
<td>78</td>
</tr>
<tr>
<td>$V_{4 Gy}$</td>
<td>59</td>
</tr>
<tr>
<td>Integral dose</td>
<td>108.9</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>$V_{5 Gy}$</td>
<td>86</td>
</tr>
<tr>
<td>$V_{10 Gy}$</td>
<td>0</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>7 Gy</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>$V_{5 Gy}$</td>
<td>51</td>
</tr>
<tr>
<td>$V_{10 Gy}$</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>6 Gy</td>
</tr>
<tr>
<td>Kidneys</td>
<td></td>
</tr>
<tr>
<td>$V_{2 Gy}$</td>
<td>98</td>
</tr>
<tr>
<td>$V_{5 Gy}$</td>
<td>62</td>
</tr>
<tr>
<td>$V_{10 Gy}$</td>
<td>1</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>6 Gy</td>
</tr>
<tr>
<td>Intestine / Bowel</td>
<td></td>
</tr>
<tr>
<td>$V_{5 Gy}$</td>
<td>65</td>
</tr>
<tr>
<td>$V_{10 Gy}$</td>
<td>0</td>
</tr>
<tr>
<td>$V_{20 Gy}$</td>
<td>0</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>6 Gy</td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
</tr>
<tr>
<td>$V_{5 Gy}$</td>
<td>100</td>
</tr>
<tr>
<td>$V_{10 Gy}$</td>
<td>99</td>
</tr>
<tr>
<td>Mean Dose</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>
There is significant sparing of normal tissues anterior to the spinal cord as a result of proton and photon beam depth dose characteristics. The differences in the PDDs are evident in the reductions in organ dose to heart, lungs, esophagus, intestine, and kidneys. Patients are treated with whole brain irradiation; therefore no advantages to structures in the head are seen when comparing IMPT and HT.

4.1.6.3 Body and Integral Dose

The body $V_{2Gy}$ and $V_{5Gy}$ dose was reduced in the IMPT plans compared to the HT plans, as shown in Table 4-8. The integral dose for the body was also lower for the IMPT plans compared to the IMRT plans.

4.2 Secondary Cancer Risk

Secondary cancer risk was calculated for all photon and IMPT plans according to the integral dose and OED models. The following section presents and compares the risk of a radiation induced secondary malignancy based on the two models.

4.2.1 Integral Dose Risk Model

The relative risk of secondary cancer was calculated for each treatment plan using the integral dose model and the results are shown in Figure 4-18.
FIGURE 4-18: Relative risk of secondary cancer per Gy of prescription dose for all patient treatment plans (red, photon plan; blue, IMPT plan)

The relative risk of secondary cancer ranged from 0.023 /Gy to 0.212 /Gy for photon plans and 0.022 /Gy to 0.115 /Gy for IMPT plans with patient 16 having the highest risk and patients 19 and 20 having the lowest risks. IMPT plans resulted in lower relative risk of secondary cancer per Gy of prescription dose than the corresponding photon plan. The relative risk of secondary cancer, per Gy of prescription dose, for proton plans was on average 0.82 ± 0.11 times the photon plan risk. Patients treated for retinoblastoma had a negligible difference in secondary cancer risk. The highest difference in secondary cancer risk was found between HT and IMPT plans for patients treated with craniospinal irradiation due to the large volume of the body irradiated with photons which does not receive dose in the proton plans. With a relative risk of 0.212 /Gy for the HT plan and 0.115 /Gy for the IMPT plan, patient 16 has the highest risk of developing secondary cancer. If such a patient were treated to 36 Gy, an irradiated patient would be 7.6 times (HT) and 4.1 times (IMPT) more likely to develop a second cancer than a non-irradiated person. Therefore if patient 16 had been treated with IMPT instead of IMRT he would have 3.5 fold reduction in second cancer risk.
4.2.2 Organ Equivalent Dose Model

4.2.2.1 Partial Brain Irradiation

4.2.2.1.1 Excess Absolute Risk

Using the organ equivalent dose model for radiation induced cancer, the excess absolute risk of secondary malignancy was calculated for all patients treated with partial brain irradiation between the time of treatment and age 80. A comparison of the excess absolute risk (EAR) of secondary cancer between HT and IMPT for a female patient treated with partial brain irradiation at age 10 is shown in Figure 4-19.

**FIGURE 4-19:** Excess absolute risk of secondary cancer for a typical patient (patient 9) for various risk models (line, Linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT based IMRT; blue, IMPT)

For patient 9, the HT plan resulted in a larger EAR than the IMPT plan for all attained ages and dose response curves. Thirty years following treatment it is predicted that there would be 51 to 53 excess cases of secondary cancers per 10000 patients/year from HT compared to 20-29 excess cases per 10000 patients/year for IMPT. Therefore it is predicted that there would be between 24 and 33 excess secondary cancers per 10000 patients/year from HT compared with IMPT.
All partial brain patients showed a reduction in the EAR of secondary cancer regardless of dose response model. Figure 4-20 shows a comparison between photon and proton EAR per 10000 patients/yr/Gy 30 years following treatment.

Figure 4-20: Excess absolute risk per Gy of secondary cancer 30 years after treatment for all partial brain irradiation patients a) Linear model, b) Linear exponential model, c) Plateau model. (bar colours: red, photon plan; blue, IMPT plan)

The EAR ranged from 0.52 per 10000 patients/yr/Gy, for patient 6 plateau model, to 2.09 per 10000/yr/Gy, for patient 7 linear model, for the photon plans and from 0.23 per 10000 patients/yr/Gy, for patient 6 plateau model, to 0.82 per 10000 patients/yr/Gy, for patient 11 plateau model for the IMPT plans. The average reduction in EAR from photon to IMPT was 0.46 ± 0.15, 0.52 ± 0.13, and 0.49 ± 0.12 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively. Patient 6 had the smallest difference in EAR for all models and the largest difference was predicted for patient 7 (linear model) and patient 11 (linear exponential and plateau model).
4.2.2.1.2 Cumulative Risk

The cumulative risk of secondary cancer per Gy for patient 9 from HT was found to be 1.00%, 0.99%, and 0.96% compared to 0.54%, 0.37%, and 0.38% for proton therapy for the linear, linear, exponential and plateau models. All risk models show a reduction in the probability that the patient will develop a radiation-induced cancer within her lifetime.

The cumulative risk of secondary cancer was lower for the proton plans compared to the photon plans for all brain patients. Figure 4-21 shows the cumulative risk of secondary for all brain patient plans.

![Cumulative Risk - Linear Model](image)

![Cumulative Risk - Linear Exponential Model](image)

![Cumulative Risk - Plateau Model](image)

**FIGURE 4-21:** Cumulative risk (% per Gy) of secondary cancer for all partial brain irradiation patients a) linear risk model, b) linear exponential risk model, c) plateau risk model. (bar colours: red, photon plan; blue, IMPT plan)

The cumulative risk of secondary cancer ranged between 0.27%/Gy and 3.14%/Gy for photon plans and 0.11%/Gy and 2.05%/Gy for IMPT plans for patient 6
and patient 7 respectively. The cumulative risk of secondary cancer per treatment Gy was lower for all proton plans compared to photon plans. Cumulative risk after proton therapy was on average $0.62 \pm 0.06$, $0.47 \pm 0.06$ and $0.50 \pm 0.07$ times the photon plan risk for the linear, linear exponential and plateau models respectively. Cumulative risk appears to decrease as age at treatment increases. Patient 3 (age 1) and patient 6 (age 19) were both treated for ependymoma. The cumulative risk for the 3 year old, using the linear exponential model, for the HT and IMPT plans were 1.33% and 0.52% per treatment Gy, respectively and the corresponding values for the 19 year old were 0.28% and 0.11% per treatment Gy, respectively.

4.2.2.2 Retinoblastoma

4.2.2.2.1 Excess Absolute Risk

Using the organ equivalent dose model for radiation induced cancer, the excess absolute risk of secondary malignancy was calculated for all patients treated for retinoblastoma between the time of treatment and age 80. A comparison of the excess absolute risk (EAR) of secondary cancer between HT and IMPT for a female patient treated for retinoblastoma at age 1 is shown in Figure 4-22.
FIGURE 4-22: Excess absolute risk of secondary cancer for a typical retinoblastoma patient (patient 19) for various risk models (line, linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT based IMRT; blue, IMPT)

The HT plan for patient 19 resulted in a slightly higher EAR compared to the IMPT plan at all attained ages and dose response models. For this patient, thirty years following treatment it is predicted that there would be 6 to 10 excess cases of secondary cancers per 10000 patients/year from IMRT compared to 4 excess cases per 10000 patients/year for IMPT. This corresponds to a reduction in the EAR from HT to IMPT of 0.03, 0.14 and 0.14 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively.

Table 4-9 gives the EAR(30) values for all retinoblastoma patients. A slight reduction in the EAR of radiation induced second malignancy was found for all compared photon and proton plans with the most reduction in risk found between the FSRT and IMPT plans.
TABLE 4-9: Excess absolute risk of secondary cancer 30 years after treatment and cumulative risk of secondary cancer within the patient’s lifetime per Gy of PTV prescription dose for retinoblastoma patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>EAR(30)</th>
<th>Cumulative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(per 10000 patients per yr per Gy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linear</td>
</tr>
<tr>
<td>19</td>
<td>HT</td>
<td>0.13</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>20</td>
<td>HT</td>
<td>0.12</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>FSRT</td>
<td>0.25</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>IMPT-2</td>
<td>0.09</td>
<td>0.08</td>
</tr>
</tbody>
</table>

4.2.2.2.2 Cumulative Risk

The cumulative risk for all retinoblastoma plans is shown in Table 4-9. The probability that a patient will develop a radiation-induced cancer within their lifetime is highest for photon therapy for all models. The largest reduction in cumulative risk of secondary malignancy was predicted for patient 20 plan 2. For this patient, the proton plan risks were 0.35, 0.18 and 0.19 times the photon risks for the linear, linear exponential and plateau models respectively. In this plan, the whole eye was irradiated compared to patient 20 plan1 and patient 19’s plan that consisted of a small PTV at the back of the eye.
4.2.2.3 Hodgkin’s Lymphoma

4.2.2.3.1 Excess Absolute Risk

The excess absolute risk of secondary cancer was calculated according to the OED model for patient 13 for both the HT plan and the IMPT plan and is shown in Figure 4-23 and Table 4-10.

**Figure 4-23:** Excess absolute risk of secondary cancer for patient 13 for various risk models (line, linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT based IMRT; blue, IMPT)
TABLE 4-10: Excess absolute risk of secondary cancer 30 years after treatment and cumulative risk of secondary cancer within the patient’s lifetime per Gy of PTV prescription dose for patient 13 for various risk models

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>EAR(30) (per 10000 patients per yr per Gy)</th>
<th>Cumulative Risk (% per Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Linear</td>
<td>Linear exponential</td>
</tr>
<tr>
<td>13</td>
<td>HT</td>
<td>1.19</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>0.82</td>
<td>0.97</td>
</tr>
</tbody>
</table>

The HT plan results in a higher EAR compared to the IMPT plan at all attained ages for all dose response models. The linear exponential model produces the largest EAR values with the linear model predicting the smallest risks. Thirty years following treatment it is predicted that there would be 25 to 33 excess cases of secondary cancers per 10000 patients/year from HT compared to 17-20 excess cases per 10000 patients/year for IMPT. This corresponds to a reduction in the EAR from HT to IMPT of 0.37, 0.58 and 0.55 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively.

4.2.2.3.2 Cumulative Risk

The risk of developing a radiation-induced cancer within the patient’s lifetime was calculated and is shown in Table 4-10. The cumulative risk of secondary cancer per treatment Gy was lower for all proton plans compared to photon plans. Proton plan risks were 0.69, 0.62 and 0.62 times the photon plan risks for the linear, linear exponential and plateau models respectively (or about 35% less).
4.2.2.4 Abdominal Irradiation

4.2.2.4.1 Excess Absolute Risk

The excess absolute risk of secondary cancer was calculated according to the OED model for patient 14 for both the HT and IMPT plans and is shown in Figure 4-24 and Table 4-11.

*FIGURE 4-24: Excess absolute risk of secondary cancer for patient 14 for various risk models (line, linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT; blue, IMPT)*
TABLE 4-11: Excess absolute risk of secondary cancer 30 years after treatment and cumulative risk of secondary cancer within the patient’s lifetime per Gy of PTV prescription dose for patient 14 for various risk models

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>EAR(30) (per 10000 patients per yr per Gy)</th>
<th>Cumulative Risk (% per Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model</td>
<td>Linear</td>
<td>Linear exponential</td>
</tr>
<tr>
<td>14</td>
<td>HT</td>
<td>0.71</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>IMPT</td>
<td>0.48</td>
<td>0.68</td>
</tr>
</tbody>
</table>

The HT plan results in a higher EAR compared to the IMPT plan at all attained ages and dose response models. The linear exponential model produced the largest EAR values with the linear model predicting the smallest. Thirty years following treatment it is predicted that there would be between 15 and 25 excess cases of secondary cancers per 10000 patients/year from HT compared to 11-23 excess cases per 10000 patients/year for IMPT. This corresponds to a reduction in the EAR from IMRT to IMPT of 0.25, 0.61 and 0.56 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively.

4.2.2.4.2 Cumulative Risk

Table 4-11 gives values for the cumulative risk of secondary cancer after radiation therapy to the abdomen. The cumulative risk of secondary cancer per treatment Gy was lower for all proton plans compared to photon plans. Proton plan risks were 0.65, 0.54 and 0.52 times the photon plan risks for the linear, linear exponential and plateau models respectively.
4.2.2.5 Pelvic Irradiation

4.2.2.5.1 Excess Absolute Risk

The excess absolute risk of secondary cancer was calculated according to the OED model for patient 12 for both the HT plan 1 and IMPT plan 1 and is shown in Figure 4-25 and Table 4-12.

![Excess Absolute Risk of Secondary Cancer](image)

**FIGURE 4-25**: Excess absolute risk of secondary cancer for patient 12 plan 1 for various risk models (line, linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT; blue, IMPT)
TABLE 4-12: Excess absolute risk of secondary cancer 30 years after treatment and cumulative risk of secondary cancer within the patient’s lifetime per Gy of PTV prescription dose for patient 12 for various risk models

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>EAR(30) (per 10000 patients per yr per Gy)</th>
<th>Cumulative Risk (% per Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model</td>
<td>Linear</td>
<td>Linear exponential</td>
</tr>
<tr>
<td>12</td>
<td>HT-1</td>
<td>0.85</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>IMPT-1</td>
<td>0.48</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>HT-2</td>
<td>0.68</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>IMPT-2</td>
<td>0.36</td>
<td>0.18</td>
</tr>
</tbody>
</table>

HT plan 1 results in a higher EAR compared to the IMPT plan 1 at all attained ages and dose response models. The linear model produces the largest EAR values with the linear exponential model predicting the smallest. Thirty years following treatment it is predicted that there would be between 32 and 43 excess cases of secondary cancers per 10000 patients/year from HT compared to 11-24 excess cases per 10000 patients/year for IMPT for plan one. This corresponds to a reduction in the EAR from HT to IMPT of 0.37, 0.41 and 0.39 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively. For plan 2, the predicted reduction in EAR from HT to IMPT was 0.31, 0.34 and 0.33 per 10000 patients/yr/Gy for the linear, linear exponential and plateau models respectively.

4.2.2.5.2 Cumulative Risk

Table 4-12 gives values for the cumulative risk of secondary cancer after radiation therapy to the pelvis. The cumulative risk of secondary cancer per treatment Gy was lower for all proton plans compared to photon plans. IMPT plan 1 had risks that were 0.56, 0.35 and 0.40 times the HT plan1 risks for the linear, linear exponential and plateau models respectively. IMPT plan2 had risks that were 0.54, 0.35 and 0.39 time the risks from HT plan 2 for the linear, linear exponential and plateau models respectively.
4.2.2.6 Craniospinal Irradiation

4.2.2.6.1 Excess Absolute Risk

Using the organ equivalent dose model for radiation induced cancer, the excess absolute risk of secondary malignancy was calculated for all patients treated with craniospinal irradiation between the time of treatment and age 80. A comparison of the excess absolute risk (EAR) of secondary cancer between HT and IMPT for a male patient treated with craniospinal irradiation at age 12 is shown in Figure 4-26.

*FIGURE 4-26: Excess absolute risk of secondary cancer for a typical CSI patient (patient 18) for various risk models (line, linear model; dashed line, linear exponential model; dotted line, plateau model) and treatment plans (red, HT; blue, IMPT)*

The HT plan resulted in a larger EAR than the IMPT plan for patient 18 at all attained ages and dose response models. Thirty years following treatment it is predicted that there would be 46 to 55 excess cases of secondary cancers per 10000 patients/year from HT compared to 17-23 excess cases per 10000 patients/year for IMPT resulting in between 22 and 38 excess secondary cancers per 10000 patients/year from HT compared with IMPT.
For all CSI patients, the EAR was larger for HT plans regardless of dose response model. Figure 4-27 shows a comparison between photon and proton EAR per 10000 patients/yr/Gy 30 years following treatment.

FIGURE 4-27: Excess absolute risk per 10000 patients per year per Gy of secondary cancer 30 years after treatment for all CSI patients a)linear risk model, b)linear exponential risk model, c) plateau risk model. (bar colours: red, photon plan; blue, IMPT plan)

The EAR(30) ranged from 1.27 per 10000 patients/yr/Gy to 2.18 per 10000 patients/yr/Gy for photons and 0.48 per 10000 patients/yr/Gy to 1.29 per 10000 patients/yr/Gy for protons. The average reduction in EAR(30) from photon to IMPT was 0.68 ± 0.17, 1.10 ± 0.20, and 1.03 ± 0.18 per 10000 patients/yr/Gy for the linear, linear exponential, and plateau models, respectively.
exponential and plateau models respectively with patient 15 having the smallest difference and patient 16 having the largest difference.

4.2.2.6.2 Cumulative Risk

For CSI patients, the cumulative risk of radiation induced secondary cancer was higher in HT plans. Figure 4-28 shows the cumulative risk of secondary cancer for HT and IMPT plans for linear, linear exponential and plateau models.

FIGURE 4-28: Cumulative risk per Gy of radiation induced secondary cancer within the patient’s lifetime for all CSI patients a) linear risk model, b) linear exponential risk model, c) plateau risk model. (bar colours: red, photon plan; blue, IMPT plan)

The cumulative risk ranged from 1.01 %/Gy to 3.1 %/Gy for HT and 0.36 %/Gy to 1.83 %/Gy for IMPT. The cumulative risk of secondary cancer per treatment Gy was
lower for all proton plans compared to photon plans. Cumulative risk after proton therapy was on average $0.56 \pm 0.10$, $0.39 \pm 0.14$ and $0.39 \pm 0.15$ times the photon plan risk for the linear, linear exponential and plateau models respectively with patient 15 having the largest difference.

4.3 References


Chapter 5:

Discussion

Modern radiotherapy techniques have resulted in increased normal tissue sparing and increased target conformity. This study has demonstrated that proton therapy can provide good target coverage while minimizing low radiation dose to normal structures that results in a reduction in the risk for radiation induced second cancers.

5.1 Treatment Planning

The target used in all IMPT plans was the same as in the corresponding photon plan. According to ICRU 78, scanning proton beams should be planned to a different PTV than in photon therapy primarily because of the proton range uncertainties(1). Typically the proton PTV is a margin placed around the CTV where distal and proximal margins are 3.5% of the water equivalent range plus 3 mm(2). The proton PTV takes into account setup uncertainties, range uncertainties and patient motion(1). Proton and photon PTVs have slightly different shapes but are both geometrical concepts that include normal tissue. As the plans were not being delivered, it was decided that in order to facilitate plan comparison, IMPT plans would be planned to the photon PTV. In our facility, the proton PTV would be slightly larger than the photon PTV therefore irradiating a slightly larger volume of normal tissue. The additional amount of normal tissue being irradiated would be small compared to the patient’s body volume and therefore the overall difference in second cancer risk would also be small.

For the dose coverage in the PTV, IMPT plans were able to achieve similar values to the photon plans for target conformity and dose homogeneity however photon plans were slightly superior in CI_{95\%} in 12 plans, CI_{100\%} in 10 and HI in 7 plans out of a total of 24 plans. Spot placement overlapping the edge of the PTV and the distal margin of 1-3mm placed on the field to account for proton range uncertainties are possible explanations for the slight over coverage of the PTV observed in many of the proton plans. The slight differences in target conformity and homogeneity observed in the target volume were minimal and may be acceptable.
Hotspots outside the target were observed in a few of the IMPT plans. Field intersection, spot placement overlapping the edge of the PTV and the distal margin on each treatment field are the most likely cause of the hotspots observed outside the PTV in IMPT plans.

IMPT plans were not able to match the target conformity and homogeneity for the retinoblastoma patients. This is in contrast to Lee et al. (3) who achieved superior target coverage with proton therapy compared to photon techniques. However Lee et al compared 3D and IMRT photon beams with protons unlike this study which compared a scanning proton beam to 3D-CRT, HT and FSRT. The inability of IMPT to conform to the target volume could be a result of the size of the spots deposited in the PTV. The lateral penumbra of each spot is larger than 2 cm, at medium energy, and is largest at shallow depths and low energies (4). The volume of the PTV used for the HT plans for patients’ 19 and 20 was 1 cm$^3$ and 0.72 cm$^3$, respectively, therefore the spots deposited in the target were larger than the target resulting in over coverage. The FSRT plan had overall better target conformity than the IMPT plan with a better CI$_{95\%}$ and an equal CI$_{100\%}$ compared to the IMPT plan.

For the organs at risk, IMPT matched or surpassed the dose sparing achieved in the photon plans for most organs for most cases. Organs at risk outside the field and distant from the PTV showed the most radiation dose sparing. Critical structures adjacent to the PTV had similar dose distributions in photon and IMPT plans because the lateral penumbra for protons and 6 MV photons is almost identical. In some cases, critical structures adjacent to the PTV have a slightly higher DVH in the IMPT plans because the dose fall-off at the end of the bragg peak cannot match the dose gradient achieved with HT.

Dose and volume irradiated are known to cause cognitive decline in children. It has been shown that a reduction in the dose and volume irradiated in the brain using protons results in a smaller decline in IQ compared with photon techniques (5-7). In this study, IMPT provided the best sparing of the brain and therefore patients would expect to see fewer cognitive late effects.

Growth inhibition in the orbital bone is a common late effect in patients treated with radiation therapy for retinoblastoma. The dose threshold for growth abnormalities is
not clear however it is believed to lie between 20 Gy and 35 Gy\(^{(8, 9)}\). Lee \textit{et al}.\(^{(3)}\) studied the compared IMRT and proton treatment techniques for retinoblastoma. The \(V_{20\text{Gy}}\) in that study were 22\% and 3\% for IMRT and protons respectively for a prescription dose of 36 Gy. In this study the \(V_{20\text{Gy}}\) was 20\% (HT) and 41\% (IMPT), 0\% (HT) and 0.3\% (IMRT), and 71\% (FSRT) and 68\% (IMPT) for patients 19, 20 plan1, and 20 plan2 respectively for a prescription dose of 45 Gy. While the prescription doses are not the same, Lee \textit{et al}. showed that protons could provide significant sparing of the orbital bone compared to IMRT, which our study did not find. This discrepancy can be attributed to the lack of target dose conformity in IMPT plans. If proton plans with equal target conformity were achieved dose sparing of the orbital bone could be improved.

For craniospinal irradiation, protons were found to achieve the best sparing of organs at risk anterior to the spinal cord as a result of the proton bragg peak. Lee \textit{et al}.\(^{(3)}\) and St. Clair \textit{et al}.\(^{(10)}\) published studies which compared protons with IMRT for the treatment of medulloblastoma. Both studies showed significant reductions in dose to the heart, liver, lungs, kidneys and esophagus and found protons to be superior to IMRT. Our study showed significant reduction in doses to the heart, liver, kidneys, lung, esophagus and bowel. In particular, radiation dose sparing of the heart could decrease the relative risk of congestive heart failure after radiotherapy, which was reported to be 1.6 per 10 Gy of thoracic radiation and 1.8 per 10 Gy of left abdominal radiation\(^{(11)}\).

IMRT delivers an increased volume of tissue outside the target low dose radiation that is of particular concern in children who may be at increased risk for the development of secondary malignancies. A study of the occurrence of secondary cancer in patients with heritable and non-heritable retinoblastoma indicated there may a threshold of 5 Gy for the incidence of an infield sarcoma\(^{(12)}\). In this study, the volume of the body receiving at least 5 Gy was significantly lower in IMPT plans for all patients, which could possibly reduced the risk of secondary malignancies.

### 5.2 Secondary Cancer Risk

The adoption of modern radiotherapy techniques, particularly IMRT, has caused the concern over the risk of radiation-induced second cancers to grow, particularly for children. The incidence of secondary cancers among long time survivors of childhood cancer is 20-30\% 30 years after treatment\(^{(13)}\). Patients treated for hereditary
Retinoblastoma have up to a 60% risk of secondary cancer by age 30-40(14). In these patients the risk of cancer is heightened through the use of radiation therapy.

The risk of secondary cancer, as predicted in this study, was higher for photon therapy compared to IMPT. The overall reduction in the risk of a radiation-induced malignancy was found to be 36% using the integral dose model and 50% using the OED model. Many studies have tried to estimate the risk of secondary malignancies after radiotherapy using various risk models. A treatment plan comparison between IMRT, 3D-CRT and IMPT of a paediatric medulloblastoma patient performed by Miralbell et al.(15) showed up to a fifteen fold reduction in secondary cancer in the IMPT plan compared to the IMRT and 3D-CRT. The risk of secondary cancer after craniospinal irradiation was also investigated by Newhauser et al.(16). Taking into account therapeutic and stray radiation fields, the risk of secondary cancer for IMRT and 3D-CRT was 7 and 12 times the risk for a scanned proton therapy and 6 and 11 times the risk of passive scattering proton therapy(16). The reduction in secondary cancer risks predicted by Miralbell et al. and Newhauser et al. were greater than those predicted in this study, where photon risks were on average 1.36 and 1.5 times greater than IMPT risks. There are several possible explanations for the discrepancy between the predicted risks. First, Miralbell et al. and Newhauser et al. used a model taken from ICRP 60(17), which is a linear no-threshold model. Secondly, the overall risk was calculated based on a sum of the risks calculated for different organs where as we calculated the total risk of secondary solid cancer in the whole body directly. Finally, Miralbell et al. studied risks in a paediatric parameningeal rhabdomyosarcoma and medulloblastoma cases and Newhauser et al. studied risks after craniospinal irradiation(CSI). Patients treated with CSI typically have large PTVs and therefore larger secondary cancer risks where as patients studied in this study had tumours in various locations with variable sizes.

An overall reduction in the risk of a radiation-induced malignancy found in this study of 36% using the integral dose model and 50% using the OED model are more comparable to those found in studies by Taddei et al.(18) and Schneider et al.(19). Taddei et al. found a lifetime absolute risk of secondary malignancy of 19.2% for IMRT and 11.4% for proton therapy for a 59-year-old patient treated for hepatocellular cancer(18). This corresponds in a 40% reduction in risk of secondary cancer for this
patient. Schneider et al. estimated that the risk of secondary malignancy, using the OED concept, in prostate patients could be reduced by as much as 50% from photon techniques to spot-scanned protons(19). Our results are in good agreement with both of these studies however Taddei et al. and Schneider et al. included doses from neutron and scatter sources, which this study did not. In addition, our study investigated risks in paediatric patients, which are expected to be higher, and over various tumour sites and sizes. The variation in PTV size and location produce a large range of integral dose outside the PTV and therefore a large range predicted secondary cancer risks.

While the models used in this study produce results that are consistent with expectations, they are based solely on the dose and volume irradiated in the treatment field. Dose from neutrons and scatter are not included in the risk calculation. Jarlskog et al.(20) investigated the lifetime cancer risks from neutrons for patients treated with passive scattering proton beams for brain lesions to 70 Gy and found that most risks were less than 1%. The conclusion was that the risk of secondary cancer from neutron sources was small but not negligible. In this study, proton plans were created using a scanned proton beam and therefore neutron dose and associated secondary cancer risks are lower than the values estimated by Jarlskog et al. It was suggested that risks caused by neutron sources were comparable to those from scatter in IMRT. In photon therapy, sources of scattered radiation are the target, flattening filter, collimators, MLC treatment head and the patient. In IMPT there are fewer sources of scatter since there are not target, scatters or collimators. As a result dose from scatter sources in photon therapy exceeds that of IMPT and therefore the risk of secondary cancer would be increased by larger extent in photon plans. Without the inclusion of scatter and neutron sources, our secondary cancer risks are an underestimate of their true value.

5.2.1 Integral Dose Model

When using the integral dose model there is a strong correlation between the size of the PTV and patient on the relative risk of secondary cancer. Risk of radiation-induced cancer depends on the volume irradiated and the dose; therefore it is not unexpected that the patients treated with craniospinal irradiation were found to have the highest risk for the development of secondary cancer. Patient 16 was found to have the highest risk of developing secondary cancer. Patient 16 is a 17-year-old male patient treated with
craniospinal irradiation and therefore has the largest PTV and is the one of the largest and oldest patients in the study. However the risk of radiation induced cancer decreases with patient age therefore patient 15, who was 3 years old at the time of treatment, should have a higher risk of secondary cancer than patient 16 who was 17 years old. A three-year-old patient has a much smaller body and therefore a smaller PTV but the relative size of the PTV compared to the whole body is large. In order to investigate the effect of the volume of the PTV and the contoured body on the relative risk, a PTV to contoured body volume ratio was multiplied to the relative risk per Gy of prescription dose for each plan. All risks were normalized to the risk of secondary cancer for patient 20 IMPT plan 1. The results are shown in Figure 5-1.

**FIGURE 5-1:** Relative risk of secondary cancer per Gy of prescription dose scaled for the ratio of the volume of the PTV to the volume of the body contour normalized to the relative risk of secondary cancer for patient 20 IMPT plan 1 (red, photon; blue, IMPT)
Modulating the risk of secondary cancer by a PTV volume to contoured body volume ratio shows that secondary cancer risk is dependent on the volume irradiated to high doses. The higher the proportion of the body irradiated to high doses, the larger the relative risk of secondary cancer. The CSI patients have the largest risk of secondary cancer with patient 15 having a risk 3000 times greater than a patient treated for a small tumour in the back of the eye.

Cancer risk is not just a function of the dose deposited in the body but is dependent on other factors such as age and genetic susceptibility. Children are more sensitive to radiation and have the higher risk of induced cancer than adults. As we age, the risk of radiation induced cancer declines therefore children who are very young at the time of treatment are more at risk for the development of secondary cancer. Children who have a paediatric cancer are often more susceptible to cancer than other children. In particular retinoblastoma patients are genetically pre-disposed to the development of cancer. In these patients the risk of cancer is heightened through the use of radiation therapy.

5.2.2 OED Model

EAR and cumulative risk decrease as age at treatment increases as illustrated by patient 15 (age 3) and patient 16 (age 17). The cumulative risk for the 3-year-old, using the linear exponential model, for the IMRT and IMPT plans were 3.10% and 1.83% per treatment Gy, respectively and the corresponding values for the 17-year-old were 1.19% and 0.36% per treatment Gy, respectively. Therefore the lifetime second cancer risk is 2.5 to 5 times greater for a 17-year-old patient than a 3-year-old. Cumulative risks are higher for younger children than older children because young children have longer post-treatment lives and their bodies are growing and changing more rapidly than older children.

Secondary cancer risk is known to be greater for larger target volumes. EARs and cumulative risks, in this study, were higher for patients with large PTVs. For example, two treatment plans were compared for patient 12 with the second plan having a lower EAR and cumulative risks for both the IMRT and IMPT plans. The main difference between the first and second plans was the target volume, which was slightly reduced in plan 2, while beam orientations and the prescription dose was the same. Therefore the
volume receiving high doses affects the EAR and cumulative risk; the larger the volume receiving the prescription dose the greater the risk of secondary cancer.

The risk of secondary cancer may also be affected by the location of the tumour with deep seated tumours creating larger cancer risks. The PTV for patient 11 is right in the centre of the brain and the proton plan consisted of three fields. These factors may have contributed to the higher EAR and cumulative risk of secondary cancer observed.

There are considerable uncertainties in the risk estimations made in this study that arise primarily from the fitted parameters used to create the model. The models were created through a combined fit from atomic bomb survivors and Hodgkin’s lymphoma patient data. There may be a lack of accuracy in the dose reconstructions performed on cohorts used to create the models. There is also known to be a genetic susceptibility for the development of Hodgkin’s lymphoma(21). It is unclear as to whether this genetic susceptibility makes them more likely to develop a second cancer(22). If Hodgkin’s lymphoma patients are at an increased risk of secondary cancer then all risks calculated with the OED model would be overestimated.

There is considerable debate about which dose-response model represents the true relationship between dose and secondary solid cancer. The true dose-response relationship is believed to lie between the linear and the linear exponential models; therefore all results were shown as a range between the two models or shown for each model separately.

5.3 References


Chapter 6:

Conclusion

6.1 Summary

Proton radiotherapy is known to reduce the radiation dose delivered to healthy, normal tissues compared to photon techniques. The increase in normal tissue sparing results in fewer acute and late effects from radiation therapy. As radiation therapy techniques improve, patients are living longer post-treatment lives therefore side effects from therapy are becoming more relevant. Late effects seen in children are particularly important because they are growing and developing. The development of secondary malignancies following radiotherapy is a well known late effect. Children are at particular risk for the development of secondary cancers as they are more sensitive to radiation than adults. The risk of the development of a radiation induced secondary cancer was calculated for paediatric patients for both IMPT and IMRT or 3D-CRT.

IMPT treatment plans were created using inverse planning in Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) with a scanning proton beam model. All proton treatment plans were created on the same CT scan as the comparable photon plan and delivered the same RBE-weighted prescription dose to the same PTV. Proton therapy plans were normalized to match the percent volume of the PTV covered by the prescription dose in the photon plans. The plans were compared for target coverage, volume of the body receiving low dose and integral dose. All patients’ IMPT plans had similar target coverage to their corresponding photon plans with the exception of the three retinoblastoma patient plans which were not as conformal or homogeneous as the HT and FSRT plans. For the most part, more normal tissue sparing was seen in the IMPT plans compared to photon techniques, particularly in the low dose regions.

The risk of secondary cancer was calculated using two methods. The first method calculates the relative risk of secondary cancer using a linear model derived from data obtained from Nguyen et al. (4). The second method is based on the organ equivalent dose concept (OED) described by Schneider et al. (5-7). The OED for the body contour was calculated from the DVH assuming three different dose-response
curves; linear, linear-exponential, and plateau. The OED was used to calculate the excess absolute risk and cumulative risk of secondary cancer.

Using the integral dose model, IMPT plans resulted in lower relative risk of secondary cancer per Gy of prescription dose than the corresponding photon plan. The relative risk of secondary cancer for proton plans was on average of $0.82 \pm 0.11$ of the photon plan relative risk. Patients treated for retinoblastoma had a negligible difference in secondary cancer risk. The highest difference in secondary cancer risk was found between HT and IMPT plans for patients treated with craniospinal irradiation due to the large volume of the body irradiated with photons which does not receive dose in the proton plans.

Using the OED model, IMPT plans resulted in lower cumulative risks of secondary cancer per Gy of prescription dose than the corresponding photon plans. Cumulative risk after proton therapy was on average $0.59 \pm 0.09$, $0.43 \pm 0.11$ and $0.59 \pm 0.11$ times the photon plan risk for the linear, linear exponential and plateau models respectively. Age at treatment and volume irradiated were factors that affected the cumulative risk of secondary cancer. Risks were higher for those patients who were young at the time of treatment and had large PTVs.

### 6.2 Future Work

In this study, secondary cancer risk was calculated for the occurrence of a solid tumour anywhere within the body contour regardless of organ or tissue. However, it is known that some organs in the body are more susceptible to cancer than others. Future work could include the calculation of organ specific secondary cancer risks. This may lead to a better estimation of the overall risk of secondary cancer and a better understanding of the benefits of IMPT.

Most secondary cancers develop within the treatment field. Outside the treatment field, the risk of secondary cancer is mainly due to scatter and neutron dose. Further work could also include a more complete estimate of the risk of a secondary cancer with the inclusion of dose from scatter and neutron sources. For 6 MV photon beams, the primary energy used in our clinic for IMRT, sources of scattered radiation are primarily leakage through the MLC and scatter within the patient. For proton therapy, neutrons are the most important source of secondary radiation. In IMPT, neutrons are produced
through proton-nuclear interactions in the patient(8). The inclusion of out-of-field risks would give a more complete comparison of the risks of secondary cancer between IMPT and photon techniques.

Finally, the implementation and validation of a technique for fast Monte Carlo calculated dose distribution could be used to evaluate the accuracy of Eclipse™ dose calculation algorithms and provide more accurate secondary cancer risks. Patient data could be re-planned, using this technology, and compared to commercially available treatment planning software. It is expected the second cancer risks calculated from Monte Carlo calculated dose distributions would be more representative of the true risks for the development of a radiation induced secondary malignancy.

6.3 References


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