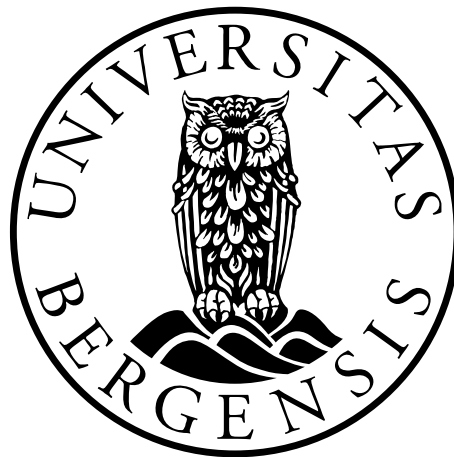# Dosimetric comparison and complication risk of estimation for photon and proton therapy of Pediatric tumors

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Acknowledgements.

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Abstract

Purpose: The aim of this study is to compare photon and proton therapy by estimating late radiation lung damage and cardiac toxicity using Dose volume-histogram, DVH metrices for both lungs and heart in terms of relative cardiac mortality and NTCP values for the heart and lungs respectively. The comparison has also been made based on the value of mean and maximum doses received by organs at risk (OARs).

Methods: Dose Volume histogram extraction has been made for 6 medulloblastoma, 3 neuroblastoma, 2 Ewing sarcoma and one rhabdomyosarcoma paediatric patients who were treated with proton therapy and re-planed in VMAT retrospectively in order to compare proton and photon treatment techniques.

Results: Proton treatment techniques reduced the mean dose to the heart and lung significantly compared to the photon treatment techniques. Due to the reduced mean dose, NTCP values for the lungs and the relative risk of cardiac mortality for the heart were reduced significantly by the proton treatment techniques. Therefore, the probability of inducing radiation pneumonitis and cardiac mortality by proton treatment techniques are very low. This probability of inducing late effects by photon treatment techniques is also very low. DVH values for the lungs show that there is little difference between proton and photon treatment techniques despite slightly higher maximum doses from protons than photons. The relative risk of cardiac mortality and DVH metrices for heart show that the heart is much spared by the proton treatment techniques compared to photons.

Conclusion: Protons treatment techniques are better than photons in sparing normal tissues based on different parameters such as NTCP and relative risk of cardiac mortality for the lung and heart, respectively. Additionally, proton therapy does not improve the DVH indices the lungs, but it does for the heart.

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List of abbreviations

RMS	Rhabdomyosarcoma
RT	Radiotherapy.
LKB	Lyman-Kutcher-Burman
ICRP	International Commission on Radiobiological Protection.
IGRT	Image Guided Radiotherapy.
IMRT	Intensity Modulated Radiotherapy.
IMPT	Intensity Modulated Proton Therapy.
LET	Linear Energy Transfer.
PT	Proton Therapy.
VMAT	Volumetric Modulated Arc therapy.
GTV	Gross Tumour Volume
CTV	Clinical Tumour Volume
PTV	Planning Tumour Volume.
DVH	Dose Volume Histogram
DNA	Deoxyribonucleic acid
OAR	Organ at Risk.
TCP	Tumour Complication Therapy.
NTCP	Normal Tissue Complication Therapy.
MLD	Mean Lung Dose.
EUD	Equivalent Uniform Dose.
PR	Radiation Pneumonitis.
CNS	Central Nervous system.

1. Introduction

«Radio therapy is 'a bad but necessary' treatment for pediatric cancer." [1]. Radiation is a major contributor for late effects but also increases the rate of survival of children with cancer. In radiotherapy, the dose is delivered to the tumour to kill the cancerous cells. This is in the form of energy deposited by ionization radiation, aiming to deliver a high radiation dose to the tumour volume while sparing the surrounding normal(healthy) tissue by keeping the dose here minimal[2]. The late effects due to the radiation dose to normal tissues can be decreased by the introduction of proton beams. Proton beam therapy may deliver 60 percent less radiation to healthy tissue around the target site compared to conventional photon radiation [3].

Even if the introduction of protons improves the treatment of pediatric malignancies, the role of photon therapy to treat child hood cancer is still crucial.

1.1 History and status of Radiotherapy

In 1895, X-rays were discovered by **Wilhelm Conrad Röntgen**. This discovery opened a door to treat malignant and benign tumors, and then after one year, the rays were used to treat breast cancer without detailed knowledge of the physical properties and biological effect of the rays.

The discovery of radium as a source of radiation in 1898 by Maria Sklodowska-Curie and her husband Pierre Curie which was followed by the report on physiologic effects of radium rays motivated scientists to study and use x-rays and radium in medicine. At this period skin cancers were the most frequently treated because of low penetration of the radiation into tissue.

In 1910s, the new device, Coolidge tube was developed which was able to emit high energy x-rays to treat deep cancers. However the results in the cancer treatment was very poor in comparison to the side effects[4].

After establishment of The International Commission on Radiological Protection, ICRP in 1928, ionisation chamber was introduced in radio therapy, RT to measure radiation dose in 1932. In this period (1930 to 1950), there has been showed a scientific progress in treating cancer due to the use of Brachy Therapy and Electron beam Therapy. Besides, the introduction of cobalt teletherapy and linear accelerator helped to treat deep tumours with better skin sparing. Currently, it is common for cancer patients to be treated by either Internal or External Radiotherapy. However, the most common RT is External Radiotherapy which include Photon and Proton therapy.

Photon therapy is a radiation therapy that uses x-rays or gamma rays produced by a linear accelerator(linac). The radiation dose is delivered at the surface of the body and goes into the body and reaches the tumor [5].This radiation therapy modality has changed in a sense of delivery techniques through time and uses advanced technology such as multi-leaf collimator, intensity -modulated radiotherapy(IMRT) and image guided radiotherapy (IGRT). Despite advanced radiation-delivery techniques, it has a limitation to deliver tumor killing radiation dose while minimizing the dose to adjacent healthy tissues. Due to this limitation of photon therapy, there is currently a high interest in the use of the proton beam radiation therapy. Proton therapy is a type of external beam radiation therapy that use ionizing radiation produced by particle accelerator which typically produce70 to 250 MeV.

 Proton therapy uses streams of protons to kill tumor cells[5]. This treatment technique can reduce the amount of radiation to healthy tissue near the tumor. To benefit proton therapy patients Pencil beam which composed Intensity Modulated Proton Therapy, IMPT and scanning beam are utilized. Pencil beams are very effective in treating the most complex tumors like brain, eye and cancer in children while effectively in sparing normal healthy tissue or Organ At Risks, OARS. Even if proton beam therapy is effective in delivering dose to the target and sparing the normal tissue, this therapy is an expensive technology.

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Even if RT is effective for local control and plays an important role in the management of childhood cancer, with the primary aim of achieving the highest likelihood of cure with lowest risk of radiation induced morbidity, children are vulnerable to RT related effects affecting normal organ functions[6]. The normal organ or tissues are affected due to exit and entry dose.

1.2 Project objectives/motivation

Even though techniques such as intensity modulated radiotherapy (IMRT), proton therapy (PT) and intensity/ volumetric modulated radiotherapy (VMAT) has allowed for improved dose conformation to the target[7], normal tissue damage can-not be completely avoided because the doses necessary to achieve tumour control usually overlap with those that can cause complications. Therefore doses that are delivered to OAR (organ at risk) may have post treatment effects[8]. The range of adverse effects seen in children is different from adults, in part due to the typical body sites affected by childhood cancer, but children are also more radiosensitive compared to adults [9]. The possible late effects or endpoints and the amount of dose received by organ at risk is also dependent on the type of treatments.

The main objectives of this thesis are to compare the doses to organ at risk from proton and photon therapy of Norwegian pediatric cancer patients, selected for proton treatments abroad and to further evaluate the potential in risk of complications for selected end points.

According to different research such as [6, 10], Proton therapy has a clear dosimetrtic advantage over photon therapy to treat pediatric malignancies. However, having dose conformity and dose distribution to normal tissue may not decrease toxicity. Some research show that no benefit is seen in hematologic toxicity, alopecia, fatigue and growth impairment if patients are treated by either of the two treatment techniques. Besides, a recent publication[11] shows that proton therapy does not improve dose

volume indices for the lungs but the again other recent publication show that the average in NTCP values were significantly lower by proton therapy[12].

2. Physics of radiation therapy

2.1 Interaction of Photons.

Photon beam and energy.

Photon beams are γ-rays. Those beams are one of the constitute of electromagnetic radiation. In context of radiation therapy, photons are considered like particles rather than waves. The energy that is carried by photons is given by E=hv, where h is Planck's constant and v is the frequency.

Photon attenuation

A photon beam produced from an accelerator or radioactive source is attenuated as it traverses matter. The attenuation is due to interaction such as absorption and scattering and the number of photons,N, after traversing a certain thickness, x, of material given by:

$$N = N_o e^{-\mu x} \qquad (2.1)$$

Where μ is the linear attenuation coefficient (units per unit distance) and its value depend on the traversed material and the energy of the photon beam.

 Photon interactions with matter

The attenuation of photon beams primarily caused by five types interaction. These are: photodisintegration (only important at very high photon energies(>10MeV)), coherent scattering, the photoelectric effect, the Compton effect and the pair production. The latter four process can be represented by its own attenuation coefficient which varies in its particular way with the energy of photon and with atomic number of the absorbing material[13]. The total attenuation coefficient for these processes is given by:

$$\mu/\rho = \sigma_{coh}/\rho + \tau/\rho + \sigma_c/\rho + \pi/\rho \qquad (2.2)$$

where σ_{coh}, τ, σ_c and π are attenuation coefficient for coherent scattering, photoelectric effect, Compton effect and pair production respectively.

Photodisintegration.

The process of emission of one or more nucleons during high- energy photon interacts with atomic nucleus is called photodisintegration. However, during this process mostly likely emission of neutrons occur. Because the rest energies of many nuclei are known for a very high accuracy, the photodisintegration process can be used as basis for energy calibration of machines producing high-energy photons[14].

2.1.3.1 Coherent scattering.

Coherent scattering interaction occur when low energy photon ($<10\,\text{keV}$) interacts with high-atomic-number of materials. Since the photon's energy is below the binding energy of the electrons of the materials, the photon can-not liberate the electron from its bound state; therefore, there is no energy transfer from photon to electron. While the low energy photon passes near the electron, the electron setting in oscillation. This oscillating electron emits an energy with the same frequency as incident photon, similarly, the scattered X-rays have the same wavelength of the incident beam. This indicates that there is no energy absorption by the medium. The only effect during this process is the change of directions (scatter) of photon or scattering of photons at small angles. As other photon interaction process, coherent scattering is represented by its attenuation coefficient, which varies in its particular way with energy of photons and with atomic number of the absorbing material. The mass attenuation coefficient of Coherent scattering, σ_{coh}/ρ is proportional to Z/(hv)

2.1.3.2 Photoelecric effect.

Unlike coherent scattering, a photon is absorbed by an atom and as result, one of its orbital electrons is ejected during the photoelectric effect interaction. The electron that is ejected (photo electron) has a kinetic energy which is the difference of the photon and binding energy of the electron$(hv - E_b)$. Photoelectric effect is probable if the incident photon energy is equal to or slightly greater than the binding energy of the

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electron. The probability of photo electric effect (mass photoelectric coefficient) is strongly dependent on atomic number. This strong dependence on atomic number is put considerable use in diagnostic imaging as it provides clear differentiation between tissues with different atomic number as well as, or in the absence of, differences in physical density[13].
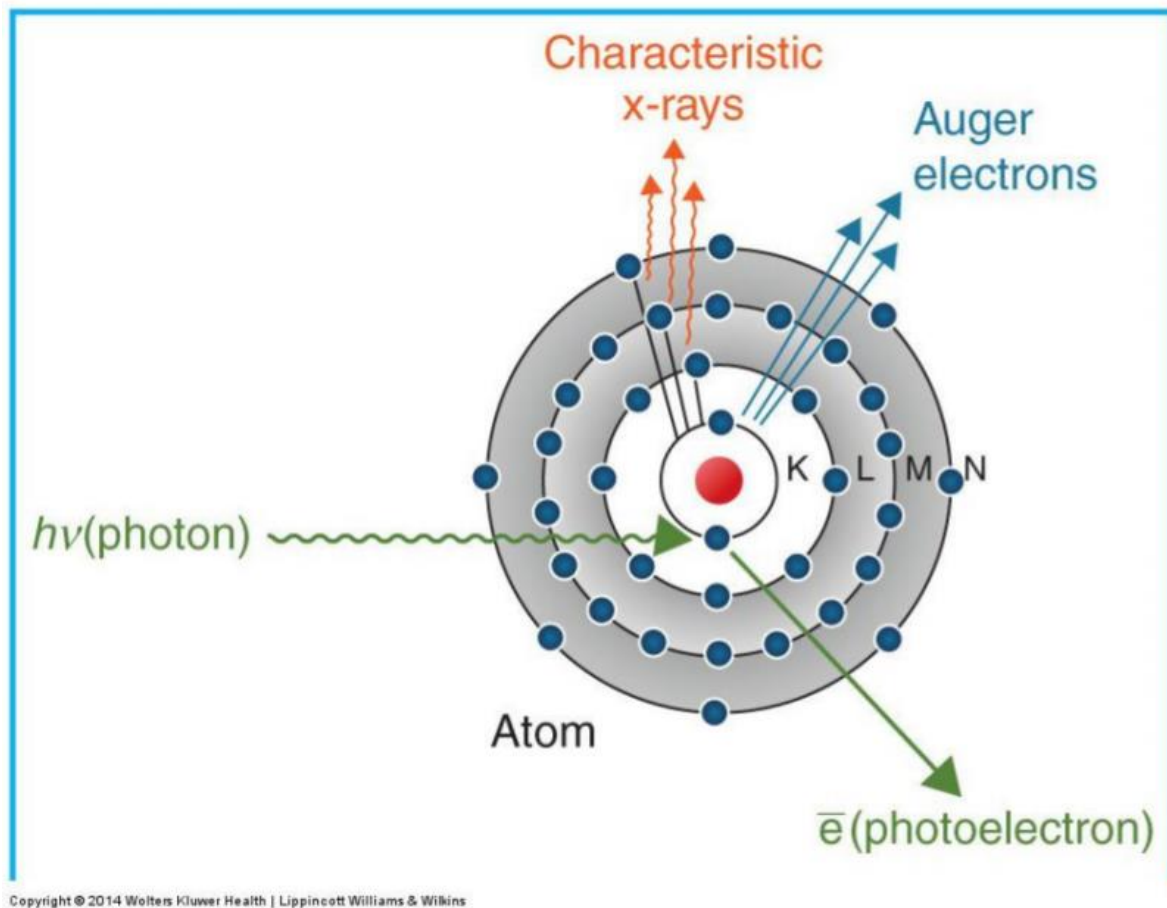
Fig.2.1 illustration of photoelectric effect[14]

2.1.3.3 Compton effect

In this interaction, the incident photon makes an interaction with atomic electron or free electrons. The photon transfers some of its energy in the form of kinetic energy to the electron in order to overcome the electron binding energy and take off it from the atom; due to the transfer of energy to the electron, the photon has lower energy after

the interaction. Unlike photoelectric effect, there is no resonance effect during this interaction. In Compton effect, the photon likely interacts with outer most shell electrons, "free" electrons with binding energy much less than the incident photons. The electron that receives an energy from the photon is emitted at an angle θ whereas the photon with reduced energy is scattered at an angle Φ. During this interaction both momentum and energy are conserved. By applying the conservation of energy and momentum, we can derive the energy of the electron and photon:

$$E = h\mathrm{v}_o \frac{\alpha(1-cos\Phi)}{1+\alpha(1-cos\Phi)} \qquad\qquad (2.3)$$

where, $h\mathrm{v}_o$ is the energy of incident photon and $\alpha = \frac{h\mathrm{v}_o}{m_e c^2}$. Where, $m_e c^2$ is the rest mass of energy. Similarly, the energy of scattered photon is given by:

$$h\mathrm{v'} = h\mathrm{v}_o \frac{1}{1+\alpha(1-cos\Phi)} \qquad\qquad (2.4)$$

where, $h\mathrm{v'}$ is the energy of scattered photon.

Unlike photoelectric effect, Compton interaction does not depend on the atomic number of the absorbing material since the interaction involves essentially free electrons in the absorbing material. This indicate Compton mass attenuation coefficient(σ_c/ρ) is independent of atomic number but depends on the number of electrons per gram.
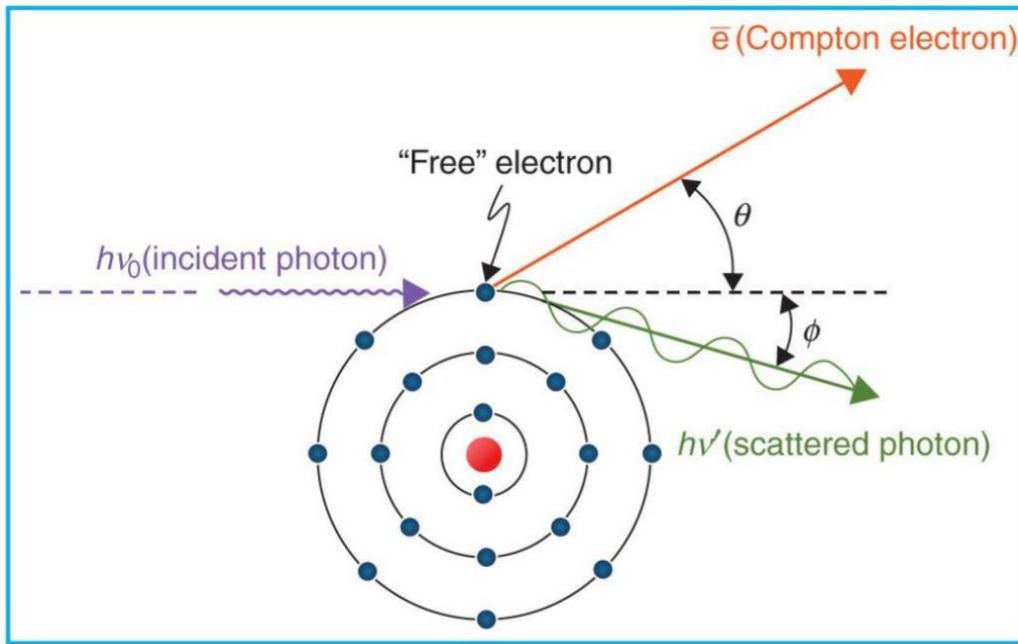
Figure 2.2 Diagram illustration the Compton effect[14]

2.1.3.4 pair production.

A photon may interact with Coulomb field of an atom in the matter through pair production if and only if the photon energy exceeds $1.02MeV$. In this process the photon vanishes and creates a pair consisting of an electron (e^-) and positron (e^+). The excess energy above the threshold of 1.02MeV will be shared by the pairs as a form of kinetic energy. The probability of a photon being absorbed by pair production is proportional to the atomic number of the material traversed and for the energy range of interest to radiotherapy, increases gradually with the incoming photon's energy[13].
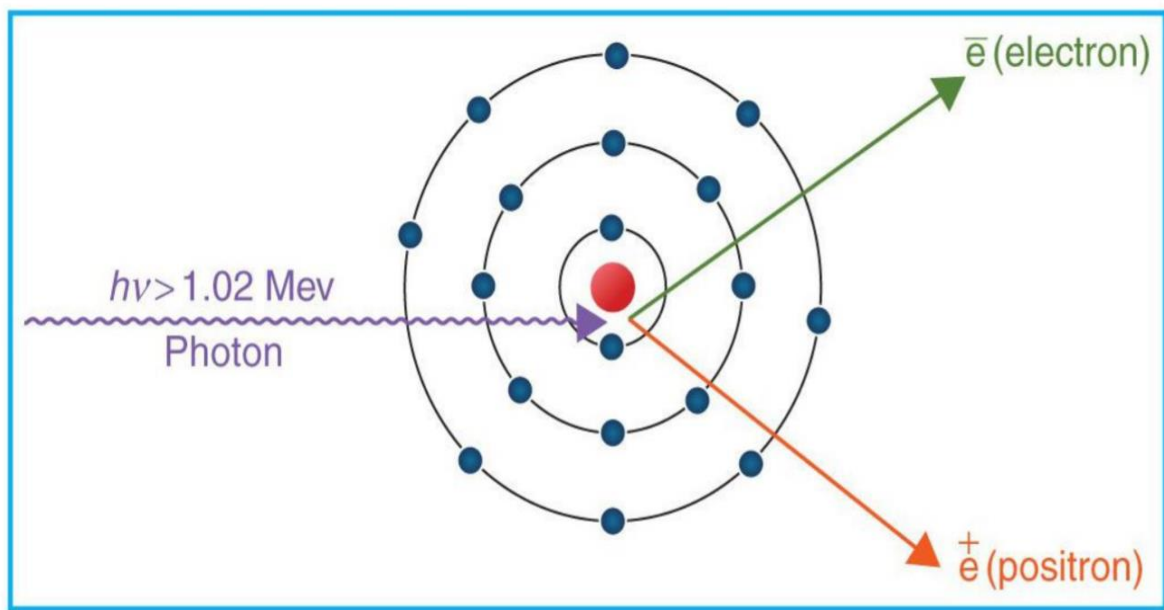
Figure 2.3 Diagram illustrating the pair production[14].

Importance of photon interaction Vs Photon energy.

As seen in the table the interaction of photons is dependent on energy regions. Photo-electric dominates in lower energy region, but pair production dominates higher energy region as Compton dominate a region which is between the two regions where one region is dominated by photo-electric and the other is dominated by pair production.

Energy regions of domination for photo-elecrtic, compton and pair production interactions	
INTERACTIONS	**LOW Z(WATER)**
Photoelectric	< 30keV
Compton	30keV to 25 MeV
Pair production	>25MeV

Table 2.1. The values of energy region where photoelectric, Compton and pair production dominates.
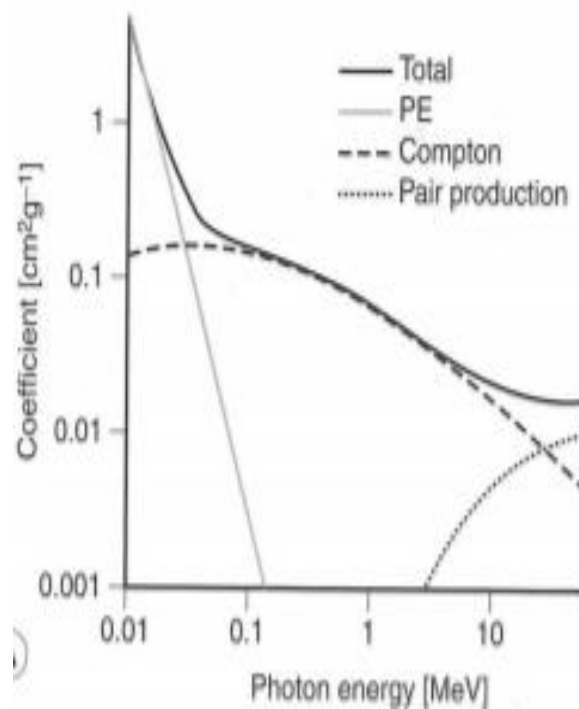
Figure.2.4 the energy range at which photoelectric effect, Compton effect and pair production are dominant in water[13].

2.2 Interaction of Proton.

Protons are considered as heavy charged particles since their rest mass of proton 938MeV is much larger than the rest mass of electron, (0.51MeV).

Protons interact primarily through inelastic Coulomb scattering with atomic electron. This interaction causes ionization and excitation and the protons lose a small amount of energy in each of numerous interactions passing through matter. Protons may also interact with the atomic nucleus through elastic or non-elastic scattering[14]. In elastic scattering, the kinetic energy of the proton that is transferred to internal structure of the nucleus is unchanged; implies the kinetic energy is conserved. Elastic scattering leads to a broadening av proton beam and leads in general to a less accurate dose deposition with depth in proton therapy. In non- elastic scattering the kinetic energy is not conserved besides the nucleus may fragmented or left in excited state. While charged particles interact with atomic nucleus, bremsstrahlung, radiative loss of energy is also

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expected or occur. Compared to interaction via inelastic Coulomb scattering, bremsstrahlung is negligible. Because, bremsstrahlung loss is inversely proportional to the square of the incoming particles mass, proton.
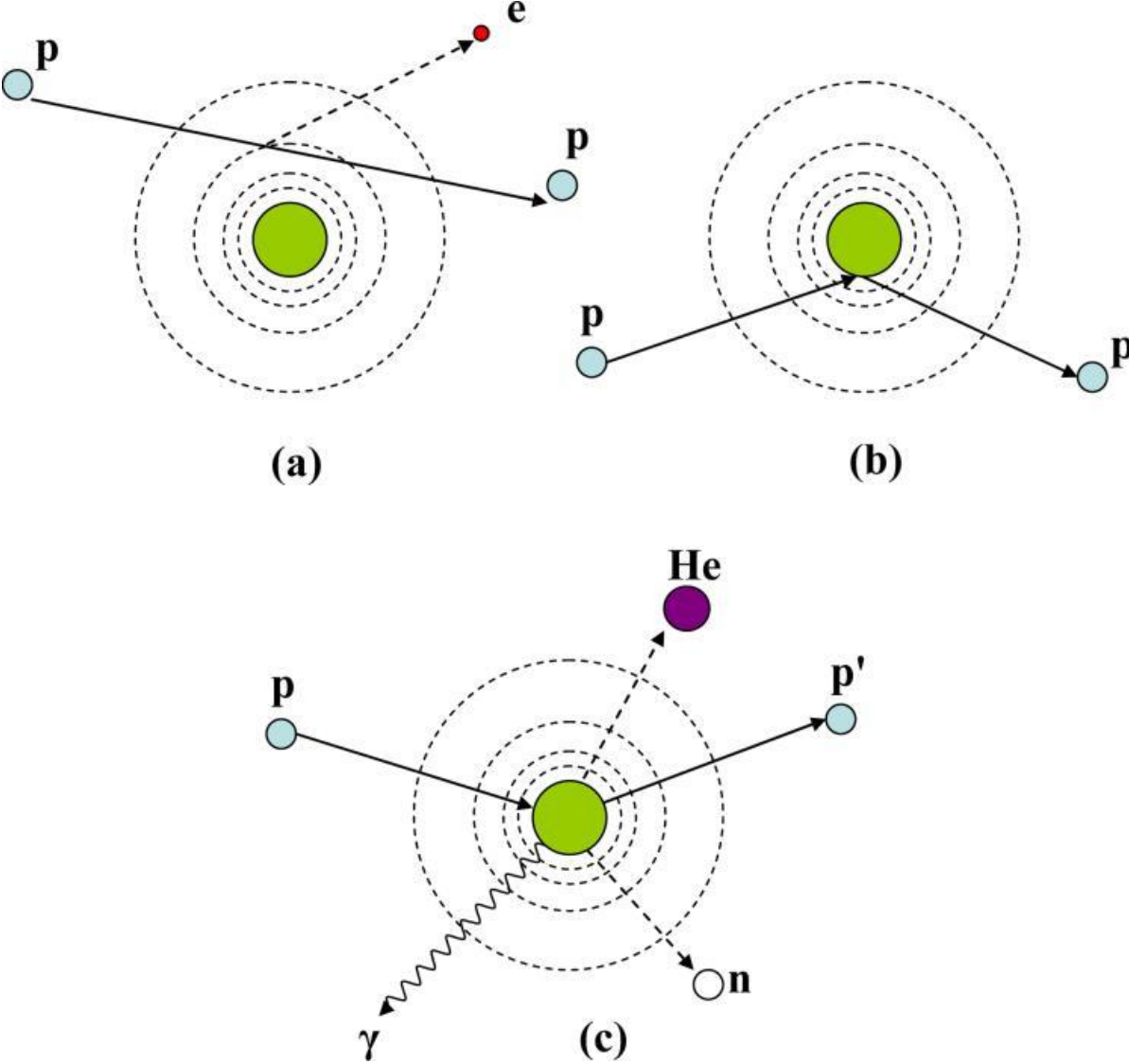
Figure 2.5 Schematic illustration of proton interaction mechanisms: (a) energy loss via coulombic interaction, (b) deflection of proton trajectory by repulsive Coulomb scattering, (c) removal of primary proton and creation of secondary particles via non-elastic nuclear interaction. (p: proton, n: neutron. He: Helium, γ: gamma rays.)[15]

Bethe-Bloch formula and energy loss rate.

The loss of energy by proton or other charged particle in elastic Coulomb scattering with atomic electron is described by Bethe-Bloch formula in terms of energy per unit length.

$$\frac{-dE}{dx} = 2\pi N_a r_e^2 m_e c^2 \rho \frac{Z}{A}\frac{z^2}{\beta^2}\left[ln\frac{2m_e\gamma^2V^2W_{max}}{I^2} - 2\beta^2 - \delta - 2\frac{C}{Z}\right] \tag{2.5}$$

Parameters in Bethe-Bloch	
N_a, Avogadro number	$\gamma = \sqrt{1 - \frac{v^2}{c^2}}$
r_e, classical electron radius	V, the velocity of incident particle
W_{max}, Maximum energy transferred.	$\frac{dE}{dx}$, energy per unit length.
m_e, mass of electron	δ, density correction
c, the speed of light	C, cell correction
ρ, the density of absorbing material	$\beta = \frac{v}{c}$
z, the charge of incident particle	A, the atomic number of the absorbing material.
Z, atomic number of absorbing material. T	I, mean excitation potential

Table2.2 Bethe- Bloch formula's parameters.

Bethe- Bloch formula indicates that the energy loss per unit length or stopping power depends on velocity and the charge of incident particle not on mass. The energy loss is inversely proportional to the square of the velocity (β^2) and directly proportional to the square particle charge (z^2)

Linear energy transfer (LET)

LET is the amount of energy deposited by ionization radiation along the particle track or in a matter and measured in $\left[kev/_{\mu m} \right]$. LET is commonly used to distinguish between ionizing radiation in relation to radiobiology; radiation having high LET (such as low-energy protons and alpha particles) will generally lead to greater biological effect than low LET radiation (photons, electrons and high-energy protons).

Range

As the protons interact with matter, they lose energy continuously since the matter is ionized by the protons during the interaction, this makes the protons to decelerate and finally stops. The finite distance travel by protons through a matter before they come to rest is known as Range. Since the difference in loss of energy by individual protons are very small, range is defined for proton beam not for a single particle. The proton range scale is roughly proportional with the square of proton energy since protons lose energy rapidly when interact with the traversing or absorbing matter. The range of charged particles including protons can be calculated by:

$$R = \frac{\pi \epsilon_o^2 \ m_e E^2}{n_a Z z^2 e^4 M} \hspace{3cm} (2.6)$$

where ϵ_o is primitivity of free space, m_e mass of electron, E is the energy of the incidence particle, n_a is Avogadro number, Z and M is a charge and mass of traversing matter respectively and e is the charge of electron.

Bragg curve

  The Bragg peak is the maximum energy deposition with depth for proton which is results due to a sharp increasing in stopping power as protons decelerate down in material. This energy deposition with depth and the continuous energy loss of the protons while the protons traversing the matter is described by depth dose curve as shown in the figure2.6.
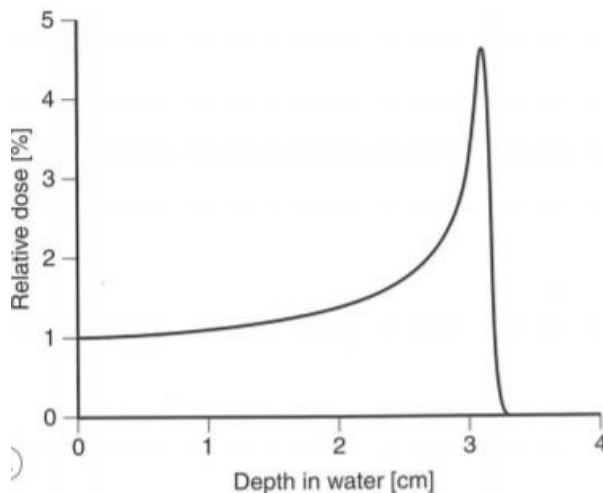
Figure 2.6. Schematic depth dose curve. Bragg peak of 60MeV protons in water[13]

Energy straggling.

The accumulation of small variations in energy loss of individual protons is called Energy straggling or range straggling which is a physical process that strongly governs the shape of a Bragg curve[15]. This physical process is helpful to understand the characteristics of proton dose distribution.
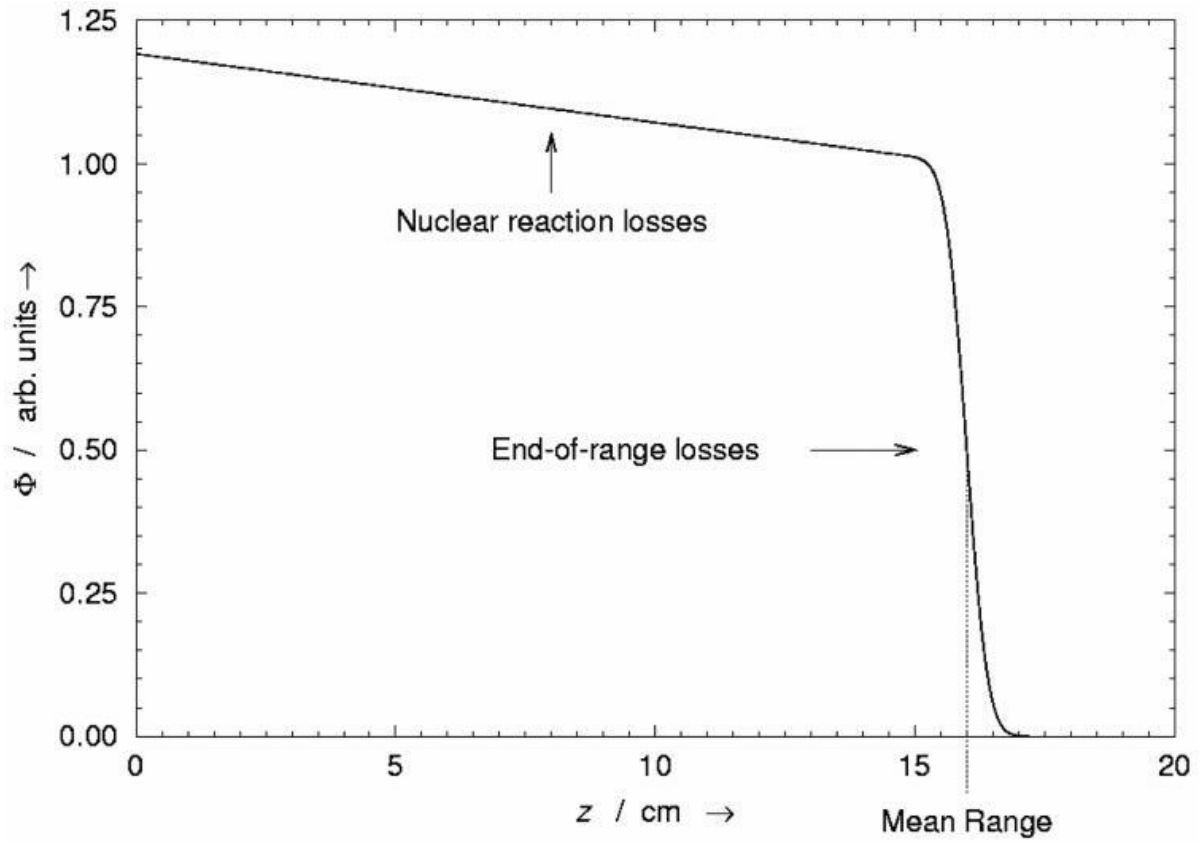
Figure 2.7. Relative fraction of the fluence in a broad beam of protons remaining as a function of depth z in water. The gradual depletion of protons from entrance to near the end of range is caused by removal of protons from nuclear reaction. The rapid fall off in the number of protons near the end of range is caused by ions running out of energy and being absorbed by the medium. The sigmoid shape of the distal falloff is caused by range straggling or by stochastic fluctuation in the energy loss of individual protons. [15]

2.3   Dosimetry

Absorbed dose

Absorbed dose represents the energy deposited in a mass by ionization radiation. It is defined as:

$D = dE/dm$, where D is absorbed dose, dE is the energy deposited and dm is the small mass. The unit of absorbed dose is Gray (Gy) which quantifies energy deposition in joules per kilogram.

Equivalent dose and effective dose.

Different degrees of biological damage can be produced by different types of radiation even if the absorbed dose is the same. The equivalent dose measures the risk the exposure of ionization radiation.

Equivalent dose is the product of absorbed dose and radiation weighting factor.

Equivalent dose$(H) = Absorbed\ dose\ (D)\ X\ Radiation\ Weighting\ Factor(W_R)$. The unit of equivalent dose is Sieverts(Sv) and Radiation weighting factor is dimensionless which is depends on the radiation energy distribution through the tissue.

Effective dose accounts for varying biological effects of different types of radiation on a particular tissue types or organ[14].

Effective dose$(H_E) = \sum W_T H_T$, where W_T is weighting factor of the tissue and H_T is the mean equivalent dose received by the tissue.

Biological effects of radiation

Exposing a body or an individual to a radiation leads to absorption of energy. This absorption can cause ionization and excitation. Besides, the absorption may cause a chemical change that form free radicals. This change that is caused by absorption may

bring a variety of biological effects in the body or individual, depending on the dose and where the dose is deposited.

People may receive radiation from different sources such as from sun and Cancer treatments. During Radiotherapy treatment, patients' body is exposed to ionization radiation. Since, RT uses ionization radiation to target and kill tumour tissue, but normal tissue can also be damaged, leading to toxicity[16]. Even if Intensity-Modulated Radiotherapy is used, there is still possibility to normal tissue toxicity. This effect, the effect that is produced by RT is classified as early radiation effect, late radiation effect and consequential radiation effect.

The early radiation effects are observed within weeks after the radiation exposure, e.g. within the first 90 days after the start of radiation therapy. This effect found in turn over tissues, like bone marrow, epidermis and gastrointestinal tract.

The late radiation effect is a chronic and the effect is found in tissues like Vascular and connective tissue components and consequential effects develop in situations where early radiation responses are associated with breakdown and loss of physiological protective barrier against mechanical or physical stress[17]. This effect found in oral cavity, Oesophagus, small and large intestine and rectum. This change, radiation effects are expressed in the person who exposed radiation but there is also a change that may not necessarily express in the individual who exposed to the radiation, but the effect can be transfer to individual's offspring. Such types of effect called Stochastic hereditary effects. The effects that is caused by this type of change could e.g. be a genetic defect. If the absorption of radiation produces an effect in the form of cancer in exposed individual, such effect is called stochastic somatic effects. The probability of stochastic somatic effects caused by radiation increases with dose. However, it is difficult to be certain that high dose exposure can cause cancer since the cause of the cancer also be another (like hereditary). If the level of the dose exceeds the threshold dose level, the effect of radiation can be acute and hazardous. Such effect is called Non-

stochastic somatic effects or deterministic. This acute effect is expressed on exposed individuals in the form of vomiting, hair loss, sterility and diarrhoea.

Since radiation exposure has negative consequences, International Commission on radiological protection (ICRP), set the standard limits to avoid or minimizing the risk radiation exposure.
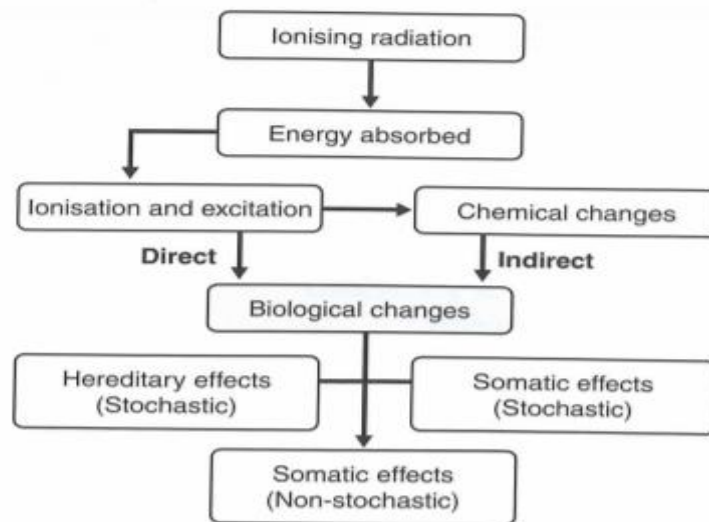
Figure. 2.8. Schematic illustration of radiation interaction and its effects [13].

Dose deposition.

As photon travel through a matter, there is high energy deposition (Linear energy transfer, LET) at the iterance of the matter and LET decreases exponentially with depth through the matter. However, protons deposit less energy in a matter while they pass through it until reach the Bragg peak where the maximum proton energy deposited. This property makes proton to increase the concentration of dose to the tumor and decrease the concentration of dose to healthy tissue as seen in figure 2.9. This makes the organs to be spared more by protons than photons.

Photons vs protons in tumors and tissues.

The physics of photons results in substantial exit dose downstream from the target, tumor which is a physical limitation of photon beam (Figure 2.9). Protons travels through tissue quickly and stop abruptly when reaching at specific depth and deposit most of their energy at the end of their path known as Bragg peak; unlike photons which deposit a large amount of their energy at close to their entrance to the region proximal to the target. Before the Bragg peak the deposited dose may be 30% of the Bragg peak maximum dose and at Bragg peak, majority of energy deposition occur then the dose falls to zero, yielding a nearly non-existence exit dose. The integral dose with proton therapy can be as much as 60% lower than photon beam techniques[18]. Thus, proton therapy delivers radiation to tumors and areas in every close proximity decreasing the integral radiation dose to normal tissues and theoretically avoiding collateral damage.

Despite Protons have an advantage over photon with fundamental issue i.e. the capability of being stopped at tumor and has low exit dose, protons are much more sensitive to tissue density as they pass through different tissues. Likewise, at greater depths the lateral margin of proton beam become less sharp due to considerable scattering[19]. Therefore, any change in tissue composition, organ motion, alteration in bone position from one treatment to the other can affect the target coverage and dose to surroundings. the disparity of dose distribution due to tissue heterogeneity is corrected by oncologist by adding a margin of uncertainty, meaning that beam is designed to overshoot the target to guarantee good coverage[20]. However, this could affect tissue-sparing advantage of protons.
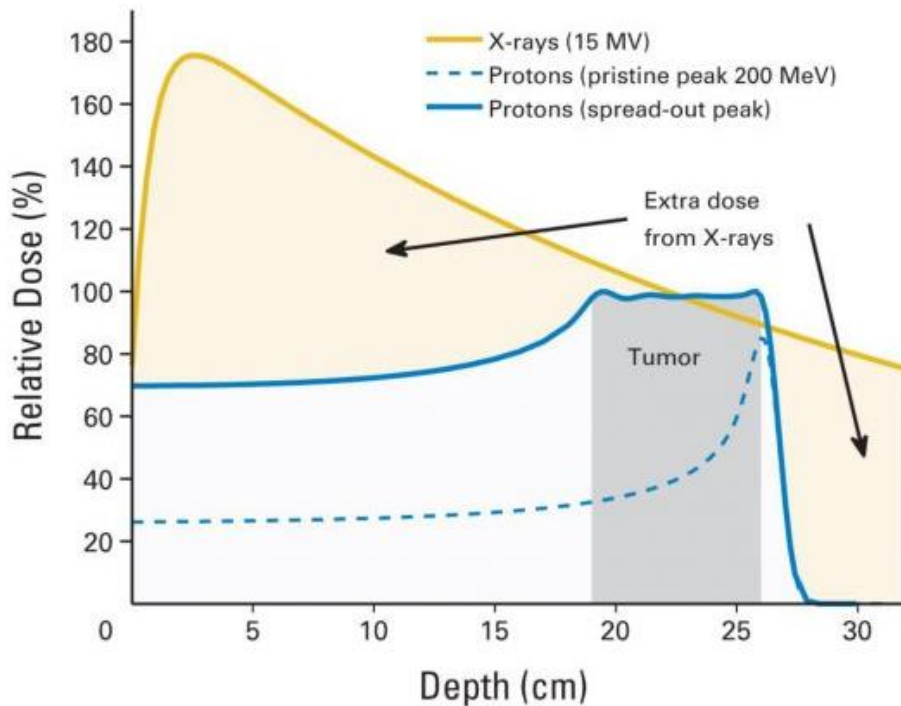
Figure 2.9. Comparison of relative depth dose distribution of photons versus protons while both beams interact with tissues and tumors[18]

2.4 Treatment planning.

Margin concepts.

The definition of tumour and target volumes for radiotherapy is vital to its successful execution since radiotherapy is a localized treatment[21]. There are several types of tumour/ target volume definition. The first is a volume that shows the position and extent of gross tumor, this volume is called Gross Tumour Volume (GTV). The second is a volume that contain GTV plus a margin for sub -clinical disease spread which therefore can-not be imaged; this is called Clinical Target Volume (CTV)[21].Planning Target Volume(PTV) is the third volume which includes GTV, CTV and margins account for set up errors and possible geometric variation. In addition, critical normal tissue structures or Organ At risk (OAR) must be considered during treatment planning, to ensure that organs can-not receive higher than safe dose.

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GTV, CTV, PTV

— Gross tumour volume
— Clinical target volume
— Planning target volume
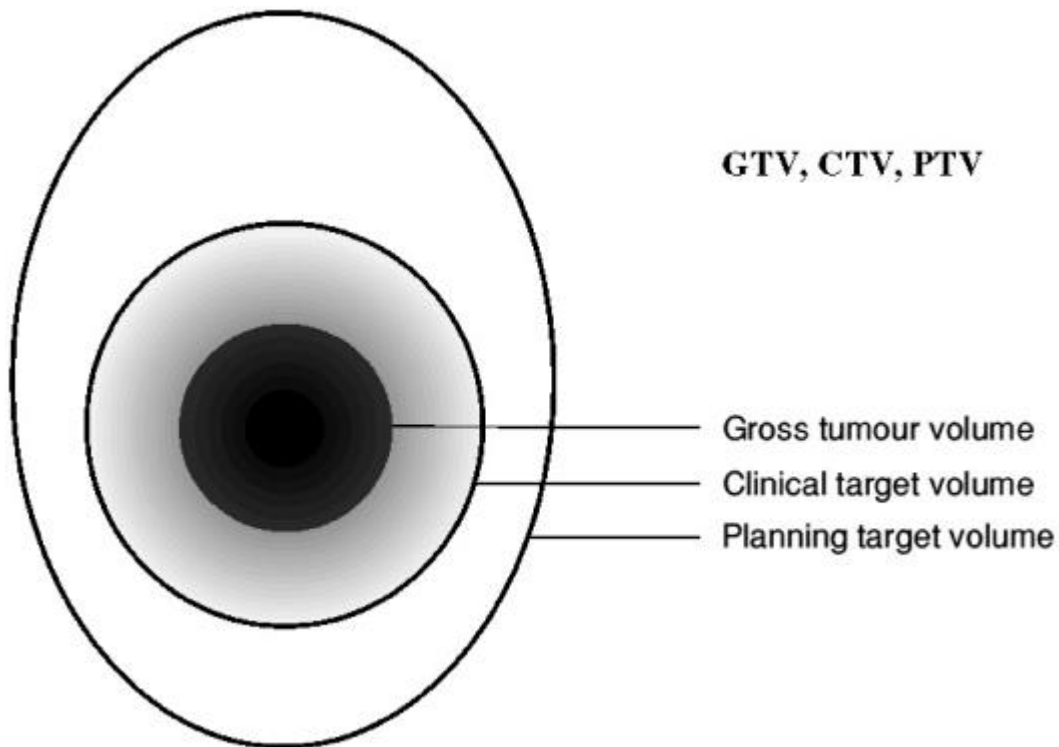
Figure.2.10. Diagram to illustrate the main radiotherapy planning volumes, taken from ICRU report 50[21].

Dose volume Histogram and Dose metrices.

The dose volume histogram (DVH) is a graphical representation of dose with in structures and it relates the amount of dose that received by the tissue and volume of the tissue. DVH can be useful to derive volume and dose metric. Volume metric (Vx[GY]) represent volume of the structure receiving $\geq$ x dose and the dose may be specified as a percent, relative to a reference dose and the desired volume may be specified in absolute units(cc) and percent. Dose metric($D_{x)}$ represent minimum dose received by X% of the organ[22].
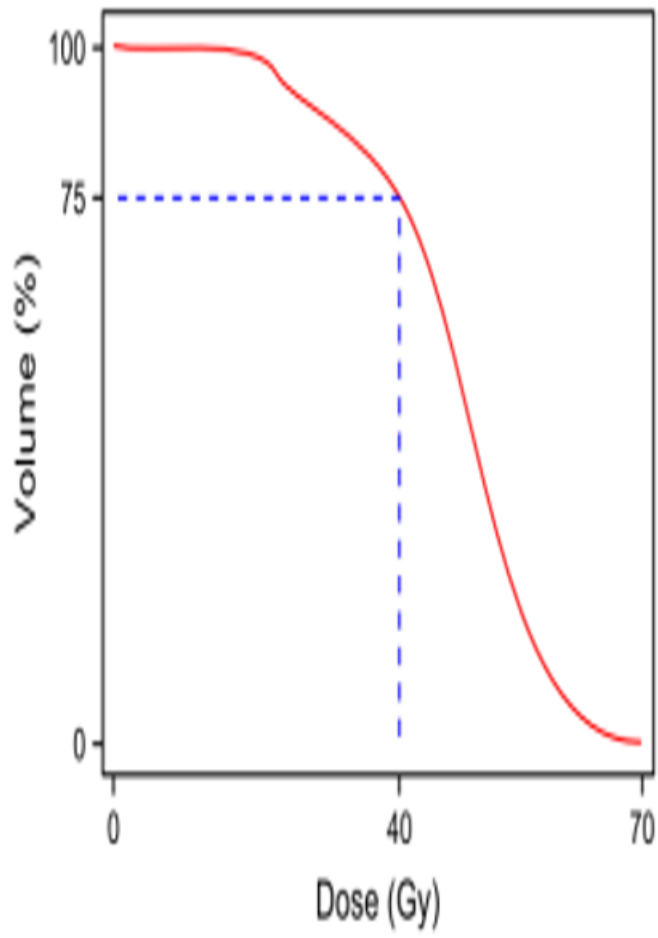
Figure 2.8. illustrate a DVH that show the volume metrics, V40Gy is equal to 75%.

3. Radiobiology.

Radiobiology is the study of how ionising radiation affects living matter[23]. This branch of science which combines the basic principle of physics and biology and is concerned with the action of ionizing radiation on biological tissues and living organisms. [24]

3.1 Ionizing and non-ionizing radaition.

An energy that is emitted in the form of energy or particle and can propagate through a medium or a space is called radiation. Radiation can be classified as ionizing and non-ionizing. Ionizing radiation can ionize a matter either directly or indirectly, but non-ionizing radiation can-not ionize a matter. Charged particles (electrons, protons, alpha particles and heavy ions) and neutral particles (photons and neutrons) are directly and indirectly ionizing radiation respectively. The quality of ionizing radiation beam is defined by LET. Typical therapeutic ionization radiation beams are:5-20Mv photons, 5-20MeV electrons or protons, the Let increases with decreasing energy as explained by the Bethe-Bloch equation.

3.2 Relative biological effectiveness(RBE).

The number of ionized biomolecules produced per unit dose of protons, heavier charged particles and X-ray is similar but the resulting biological effects substantially differ[25].The difference in biological effectiveness such as cell killing, tissue damage, mutation and carcinogenesis are characterized by RBE which is the ratio of the dose of reference radiation (typically photons) to produce a specified effect to the dose of test radiation to the same effect.
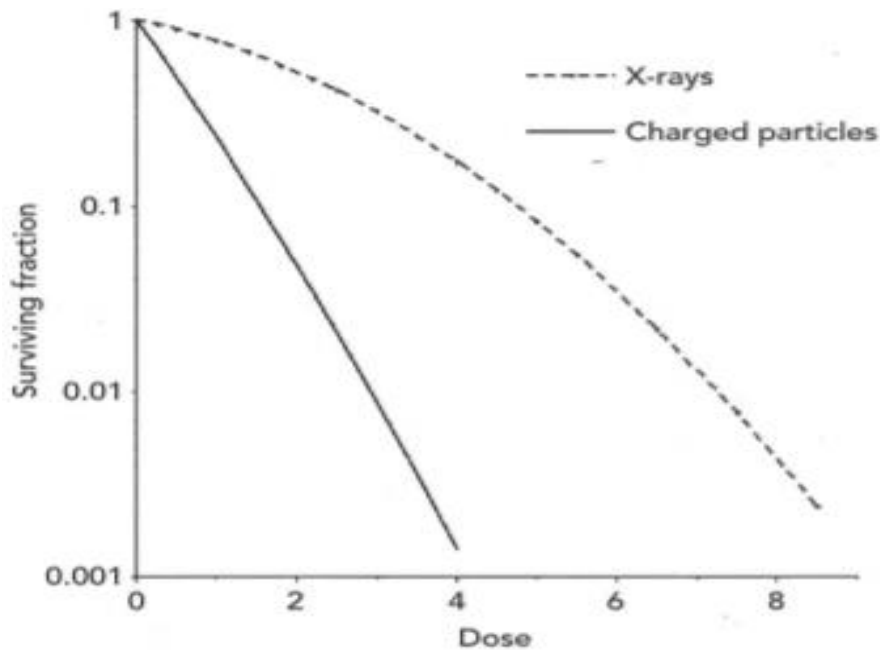
Figure 3.1 The fraction of cells surviving a particular dose of X-rays is larger than the fraction of cells surviving the same dose of charged particles such as protons and carbon ions[25].

In proton therapy a constant RBE of 1.1 is assumed clinically. The prescribed absorbed dose in proton therapy is then slightly lower than for photon therapy. The RBE-weighted dose can be calculated as:

RBE-weighted dose = 1.1 x absorbed dose.

The units of RBE-weighted dose is Gy (RBE)

3.3 Cells and irradiation.

Cells are radiosensitive. When cells are exposed to ionizing radiation, biological damage of cells function occur. This biological damage of cells functions mainly from damage to DNA. When this radiation interacts with DNA, it makes DNA's either single or double strand to be broken. The double strand DNA breaks occur when enough energy (LET) is deposited in the DNA. Damage of the DNA of the cell can cause the

cell of death or genetic mutation that may lead to cancer induction (Carcinogenesis)[26]. .

3.4 Linear quadratic model(LQ)

The LQ model is the most often used cell survival model which relates the fraction of irradiated cell $S(D)$ that maintain their reproductive integrity and a delivered dose, D (figure3.2.)
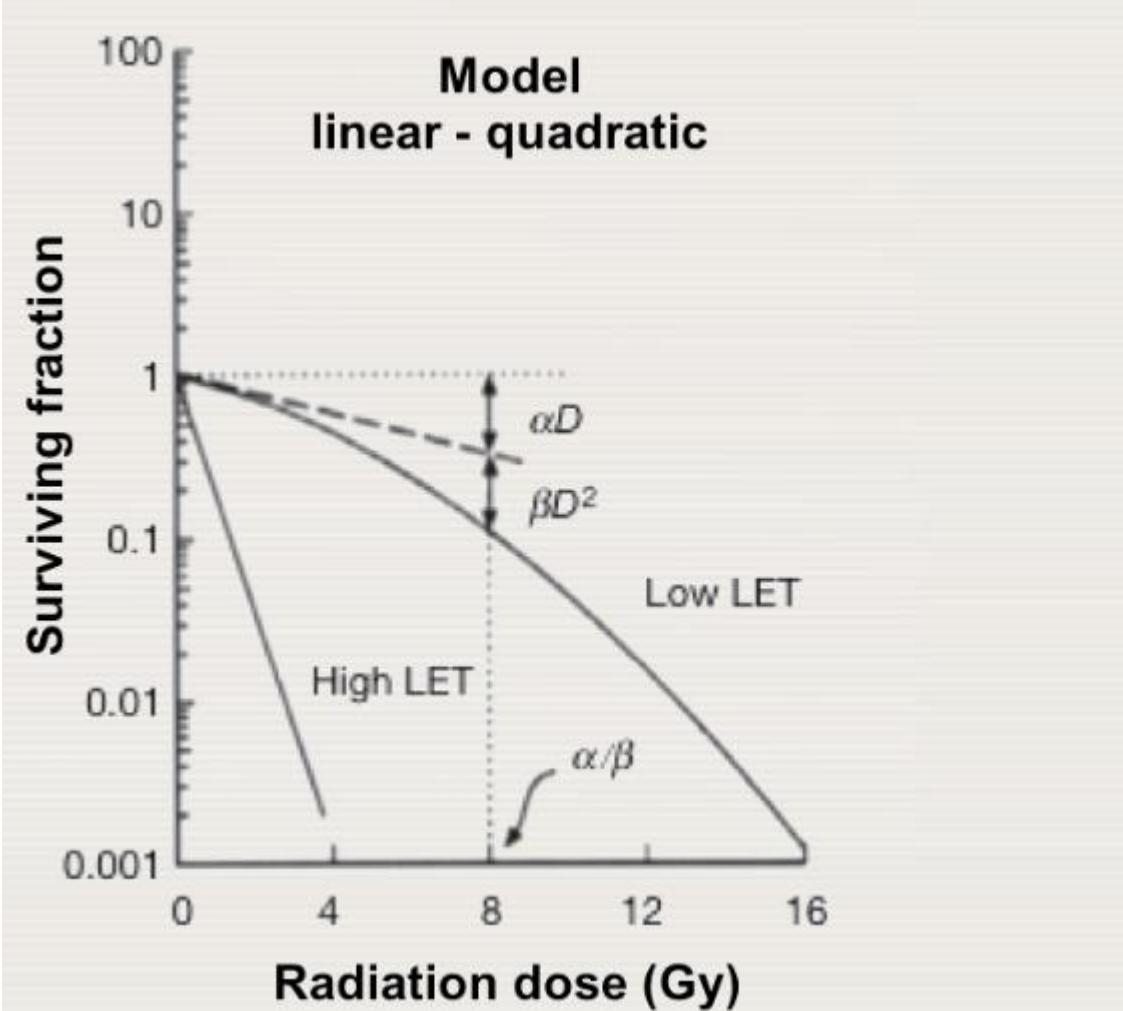
Figure 3.2. The linear quadratic model with different parameters. For high LET, the cell survival curve is almost an exponential function of dose and for low LET, the

survival curve shows the initial slope followed by shoulder region and become nearly straight line [27].

The survival probability of cell, $S(D)$ following to a single exposure dose, D radiation is described as:

$S = e^{\alpha D - \beta D^2}$, where α and β are parameters describing the cell's radiosensitive and D is the dose to which it is exposed.   As the survival fraction is plotted against dose in log scale which is illustrated in figure 3.1, it shows α dominates the initial region at low doses and followed by increasing curvature as a quadratic β more dominant. The degree of curvature is frequently defined in terms of α/β ratio in Gy. This ratio corresponds to the dose at which the linear and quadratic contribution are equal. Thus, cells with high α/β ratios see relatively constant rate of cell killing with increasing dose, while those with low α/β ratio shows a pronounced curve[28].

3.5 Therapeutic ratio.

Therapeutic ratio shows the relationship between tumor control and the likelihood of normal tissue complication or morbidity. The balance between the probability of tumor control(TCP) and the risk of normal tissue complication, NTCP is a measure of therapeutic ratio of the radiotherapy treatment[8].

Tumour control probability(TCP).

TCP is the probability that a given dose of radiation will provide eradication of biological cells of tumor. TCP is described by a dose-response curve which is defined by a sigmoidal function and TCP shows the response of tumor cells to radiation.

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Normal tissue control probability(NTCP).

The probability that a given dose of radiation will cause an organ or structure to experience complication is called NTCP.As TCP, a dose response curve which is defined by sigmoidal function describe NTCP.

To achieve a high probability of tumor control at low NTCP is the aim of radiotherapy.
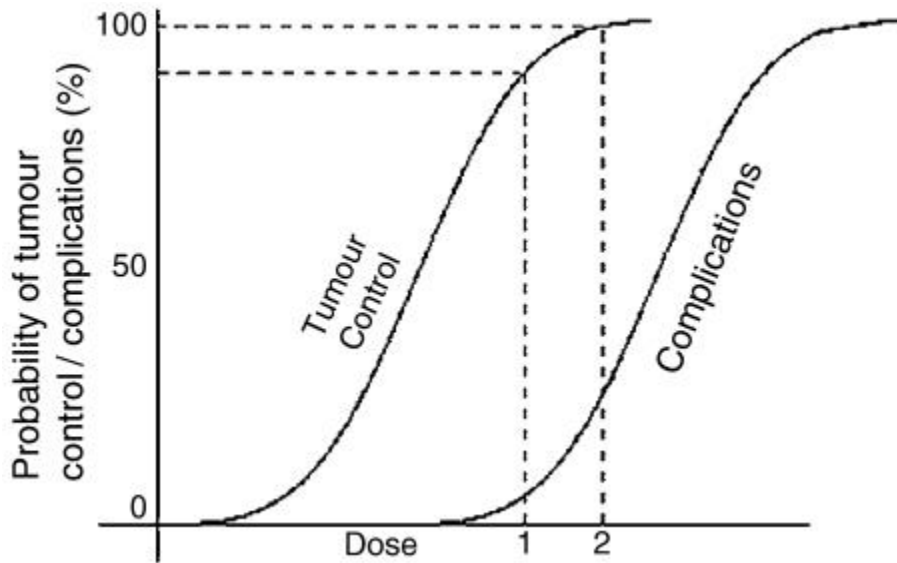
Figure 3.3 Idealized -response curve. For increase in dose from level 1 to 2 there is small increase in tumour control but much larger increase in treatment complication probability[8].

4. Materials and methods.

4.1 Patient data and treatment planning

Patient data.

Twelve pediatric tumour patients (6 Medulloblastoma, 3 neuroblastoma, 2 Ewing sarcoma and 1 Rhabdomyosarcoma, age range 2-16 years) were included in this thesis. These patients, 8 males and 3 females were treated with protons in University of Florida Health proton therapy institute in America between 2014 and 2016; and one Medulloblastoma patient was treated in Heidelberg Ion beam Therapy Center in Germany in 2015.

For the purpose of this thesis, for each patient, VMAT plans were used for comparison to the delivered PT plans. Dose-volume histogram (DVH) extraction for target volumes and organ at risks was performed in Haukeland University of Hospital.

Table.4.1. Patient and Tumuor characteristics (n=12). M=Male, F= Female, Age = Age during treatment period.

Diagnosis	Patient number	Region in body	Dose (Gy)
Medulloblastoma	P2	Brain/CSI	54
Medulloblastoma	P3	Brain/CSI	54
Medulloblastoma	P5	Brain/CSI	54
Medulloblastoma	P6	Brain/CSI	54
Medulloblastoma	P9	Brain/CSI	54
Medulloblastoma	P10	Brain/CSI	54

Neuroblastoma	P7	Abdomen	21
Neuroblastoma	P11	Craniospinal	21
Neuroblastoma	P12	Craniospinal	21
Ewing sarcoma	P4	Abdomen	54
Ewing sarcoma	P8	Abdomen	50.4
Rhabdomyosarcoma	P1	Abdomen	50.4

RT planning, Treatment techniques and delivery.

The patients were treated with protons and re-planned in VMAT retrospectively at hospital in Norway for the purpose of comparing the delivered proton plans. The patients were treated with protons, either passive scattering or IMPT, the re-plannings were done with photons beam data from Varian true beam and Elekta synergy. and the patients were also CT scanned in treatment position; for treatment planning. The radio therapy treatment plans were calculated using the Eclipse treatment planning platform.

Among six Medulloblastoma patients, for five patients 23.4 Gy was prescribed to the entire PTV and additional 30.6 Gy to the boost PTV; therefore, the total tumour dose 54Gy was delivered in 30 fractions. Similarly, for one patient also the prescribed dose was 36Gy and additionally, 18Gy was given to Boost PTV. The total tumour dose for this patient also 54Gy in 30 fractions. In order to allow uniform dose distribution tissues which are parts of central Nervous system (CNS) are considered as a secondary target in Medulloblastoma patients since they found close to PTV. For Medulloblastoma patients, all protons plans were delivered 3-7fields using 3mm margins for the P TV[29] .

The three Neuroblastoma patients were prescribed total dose of 21Gy with 14 fractions. For these patients, the clinical target volume, CTV include the GTV plus anatomical

confined 1.0-1.5cm margin. The two Ewing sarcoma patients were prescribed the total dose of 50.4Gy and 54 Gy. For the former, the total dose was delivered in 28 fractions whereas for the latter, the total dose was delivered in hyper fractionated RT method, i.e. the patient received 1.5Gy two times a day in 18 fractions. For Ewing sarcoma, there are two GTVs (GTV1 and GTV2) and the CTVs include GTV plus 1cm with high threshold to reduce the volume for pushing margins. The prescribed dose for Rhabdomyosarcoma was 41.4Gy but additionally 9Gy was delivered for to boost PTV. Therefore, 50.4Gy was the total dose prescribed dose. As Ewing Sarcoma, the RMS plan also contain two GTVs: GTV1 and GTV2.The former consisted pre- chemo tumor accounting for pushing margins and infiltrating margins that recede. The latter consisted the post chemo nodes, pre surgical disease.

The planning goal which is normally 99% of the prescription dose to the CTV target volume but most importantly the target dose of the photon plan was scaled to fit the CTV of the delivered proton treatment.

Target volume, PTV and OAR delineation for all patients were done at treating institute besides, all structures were reviewed by an experienced oncologist.

Doses for OAR, DVH analysis and Toxicity.

Children treated with photon therapy and proton therapy for tumor have a risk that OARs can be delivered excess dose. DVH(Dose-volume-histogram) files of the patients was extracted, used and analysed in order to compare the doses; mean, maximum and minimum dose that was delivered for lungs and hearts. Besides, late acute and late toxicity, radiation pneumonitis and cardiac toxicity to lungs and hearts respectively; because of proton and photon therapy were compared and estimated based on Tolerance of Normal Tissue to Therapeutic radiation, NTCP values that was calculated by using LKB model and relative risk of cardiac modelling (RR).

Radiotherapy-derived parameters.

Normal tissue in the chest, including the healthy lungs, esophagus, heart, brachial plexus and spinal cord are often limiting the dose of radiotherapy[21]. To limit the dose to normal tissues, Radiotherapy-derived parameters are used. Such as $V_5 \leq 65\%$, $V_{20} \leq$ 30-35% and mean dose ≤ 7 Gy for lungs and for heart, the dose constraints $V_{25} \leq 10\%$ are used. Based on those DVH metrices, the proton and photon therapy are compared, and the possible late effects also estimated too.

Lyman-Kutcher-Burman(LKB) model for lung NTCP.

The 3D dose distribution in a patient is used to determine DVH of organs which is normally the basis of calculating NTCP.

In this thesis Lyman-Kutcher-Burman (LKB) model was used to calculate NTCP of lungs with the endpoints radiation pneumonitis. In general, LKB model are based on based on the equivalent uniform dose (EUD) which has a power-law relationship with local-dose effect relation.

$$EUD = (\sum D_i^{\frac{1}{n}} \frac{V_i}{V_{tot}})^n \qquad (1)$$

Where V_i is the volume irradiated with dose D_i in bin number I and V_{tot} is the volume of the organ.

In this thesis a LKB based lung NTCP radiation pneumonitis model by Seppenwoolde et al[30] was used. In this model, n=1 is used, simplifying equation (1) to:

$$EUD = \sum_i D_i \frac{V_i}{V_{tot}} = MLD \qquad (2)$$

 Where MLD is the mean lung dose. According to LKB model NTCP is calculated using:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \qquad (3)$$

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Where t is defined as:

$$t = \frac{MLD - TD_{50}}{m TD_{50}} \qquad (4)$$

where TD_{50} is the uniform dose given to the entire organ volume that results in 50% complication risk, m is a measure of the slope of the sigmoid curve represented by integral of the normal distribution[31].The value of TD_{50} and m is 30.8Gy and 0.37 respectively, according to Seppenwoolde[30].

Relative risk of cardiac mortality.

The risk of cardiac mortality was estimated based on extracted DVH data and model by Tukenova et al[32]   after RT, the NTCP values for heart were not calculated since the risk of radiation induced valvular diseases can-not be modelling using NTCP models only based on heart-dose volume distribution[33]. Therefore; instead of NTCP modelling relative risk of cardiac modelling (RR) is calculated.

The dose effect relationship between the average radiation dose received by the heart and cardiac mortality was modelled with linear equation 1 of the excess RR(ERR)[32]

Therefore, a linear relationship between the mean radiation dose to the heart and the relative risk of cardiac mortality is given by:

$$RR = 1 + \alpha_1 D \qquad (5)$$

where RR is the relative risk, H

D is the mean heart dose, α_1 the linear coefficient whose value is 0.6(95% confidence interval, 0.2-2.5)[34].

The ratio of relative risk (RRR) of cardiac mortality was defined as:

$$RRR = \left. RR_{pr} \middle/ RR_{ph} \right. \qquad (6)$$

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where subscript Pr and ph denote Proton and Photon therapy respectively.

Statistical analysis.

For dosimetric comparison of proton beams to advanced radiotherapy (VMAT) dosimetric values, V_x and D_x are calculated and used based on the DVH of the lungs and heart of each patients and the bar graph that shows the mean dose comparison of the treatment techniques with their corresponding median value was plotted. In order to calculate NTCP values for both treatment techniques (for lung), (3) is used and based on the results of NTCP values both treatment techniques are compared, and possible radiation pneumonitis are also estimated. However, for heart, instead of calculating NTCP values, relative risk of cardiac mortality (RR) and the ratio of relative risk (RRR) of cardiac mortality were calculated, using (4) and (5) and based on the results the possible cardiac mortality is estimated as well as estimating which one of the two treatment plans have a likely possibility to produce toxicity. The Dose-Volume histogram of the lungs and hearts were not corrected for dose per fraction effect because the dose per fraction for the patients is 1.8Gy which is close to the standard 2Gy fractions. Therefore, the mean dose of the lungs from Dose-volume histogram was used as mean lung dose (MLD) to calculate NTCP and heart mean dose is used to calculate relative cardiac mortality for heart.

5. Results

The aim of the treatment plan is to deliver prescribed dose to the tumour and minimum dose to the normal tissue, OAR. Based on this principle, the planning target volumes, PTVs coverage for photon were in a range of 99.7% to 100.1% and for protons, the coverage was in a range of 99.3% to 100%. The photon and proton treatments may therefore be expected to produce similar TCP values. The difference in treatments is therefore mainly in dose received by the OARs and will be presented in the following.

5.1 Lung doses.

DVH metrices

DVHs for the lungs are shown for all patients in figure 5.1. In general, we see that the lung doses were highly heterogenous with maximum doses of several tenths of Gy for some patients. Moreover, as table A.1. shows, generally, the larger portion of the lung received a smaller amount of dose by proton than photon, but the smaller portion of the organ got smaller dose from photon than proton. In other words, protons spare the lungs for low to intermediate doses much better than photons whereas photons spare the lung for high doses slightly better than protons. This can be seen for patient P5 in figure 5.2. This is also clearly seen from DVH metrices such as V_{15}, D_{40}, and V_5.

Of 6 medulloblastoma patients, 108.41cc and 42cc of the lung of two patients, P2 and P5 respectively received 15Gy (V_{15}) and more from proton but the same amount of dose was received by 99.44cc and 31.70cc of the lung of the same patient from photon. However, 40% of the lung of the two-patients received a minimum of $0.08Gy(D_{40})$ from proton and $4.99Gy(D_{40})$ and $4.8Gy(D_{40})$ from photon. As table A.1. shows also for the rest of three medulloblastoma patients has also the same trend with different dose metric parameter but with the same volumetric parameter. Similarly, V5 and V21.5 of lung for the neuroblastoma patients that is produced by photon is smaller than protons and D_{40} that is produced by photon larger than proton. And the same is

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applicable for Ewing sarcoma patient with different DVH metric. The lung dose for three patients, P1, P4 and P7 were not discussed since the amount of dose that was delivered by both techniques is insignificant.
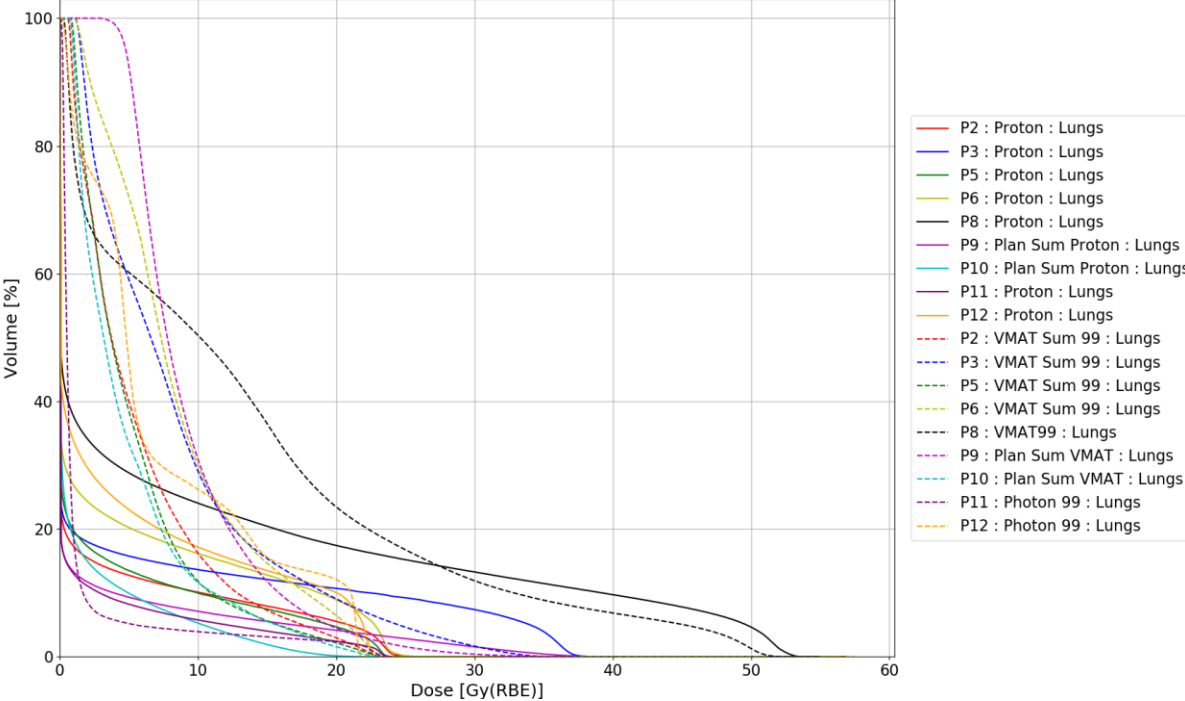
Figure. 5.1 A plot that shows the dose to lungs by proton and photon with their corresponding treatments plan. Proton doses are indicated by solid lines while photon doses are shown using dash lines.
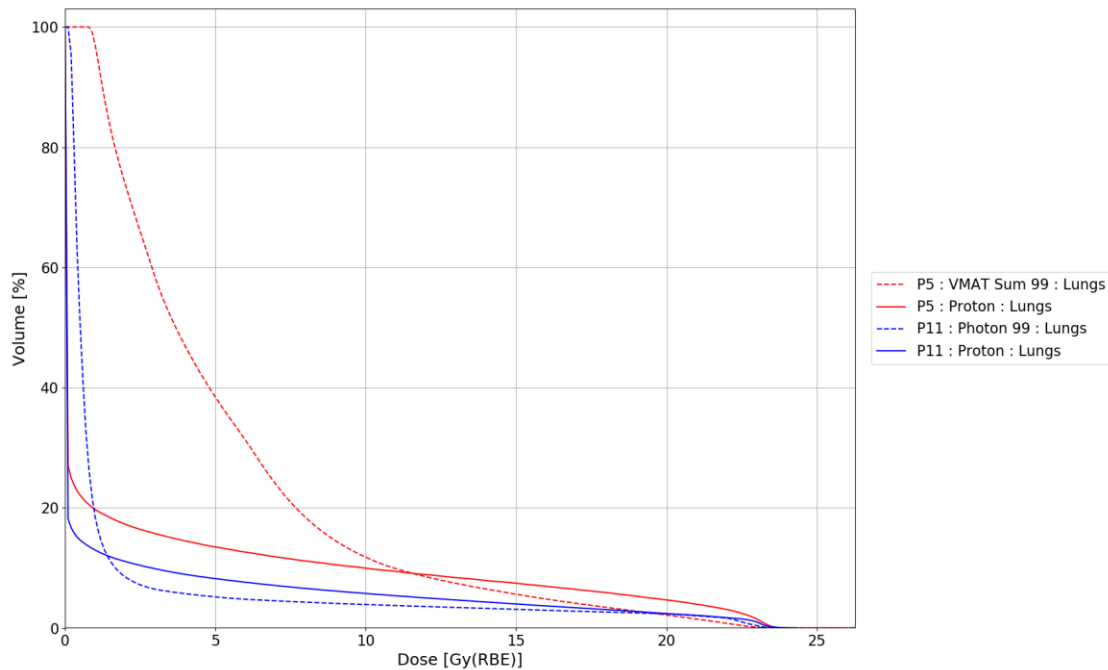
Figure.5.2. A plot shows the region (dose>12Gy, approximately) where photon's dose to a medulloblastoma patient(P5) is less than proton's dose(red) and the region (Dose>1.5Gy, approximately) where photon's dose to a neuroblastoma patient(P11) is less than proton's dose(blue). Proton doses are indicated by the solid lines while photon doses are shown using dashed lines.

Mean dose.

According to the bar graph, figure-5.2 below, the mean dose of photons is consistently greater than protons. Protons typically decrease the mean dose of lungs by almost a factor of two and for one medulloblastoma patient (P9) the dose is reduced almost by a factor of 5. For one neuroblastoma patient (P10), the mean dose for two plans have no significance difference whereas the mean dose for other patient is significantly decreases by proton. For Ewing sarcoma also the difference is visible i.e. proton decreases the mean dose significantly. One neuroblastoma, RMS and Ewing sarcoma patient have not been delivered significant dose by both treatment techniques.

As we see from Figure 5.2. the value of mean dose separating the higher half from the lower half of the dose, median of the mean proton is 2.3 Gy and photon's is 7.2Gy.
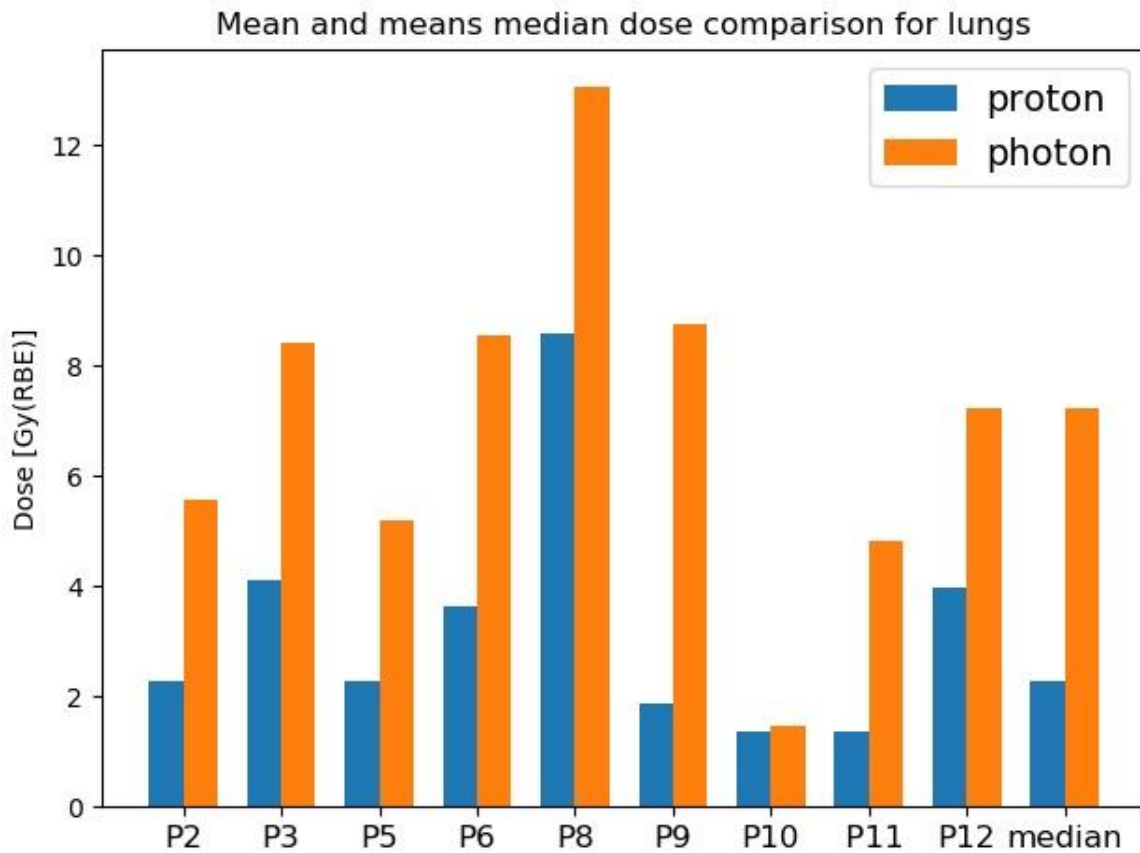
Figure 5.3. Comparison of mean dose of proton and photon to the lungs. The median mean doses are displayed in the last bars.

According to Tolerance of Normal Tissue to Therapeutic Radiation of Dr. Emami B et al [22], one Ewing sarcoma patient(P8) got a mean dose of 8.577Gy from proton therefore, the incidence of pneumonitis to be appeared is between 5 and 10%. The incidence of pneumonitis to be appeared to this patient is 10% due to the delivery of radiation from photon. The incidence of pneumonitis to be appeared in these 4 patients (P3, P6, P9 and P12) is 5% due to the delivery of photons.

Maximum dose.

Figure 5.3 and figure D.1 show that the maximum doses which were delivered to the lungs by protons is larger than photons for 7 of 9 patients. The value of the maximum dose for the other two patients from photons are slightly larger than protons. Therefore, the maximum dose values comparison and DVH metrices reveals that in terms of restricting maximum dose photons are better than protons. The maximum dose of the RMS patient(P1), one Ewing sarcoma(P4) and one neuroblastoma(P7) were not included since the dose is insignificant.
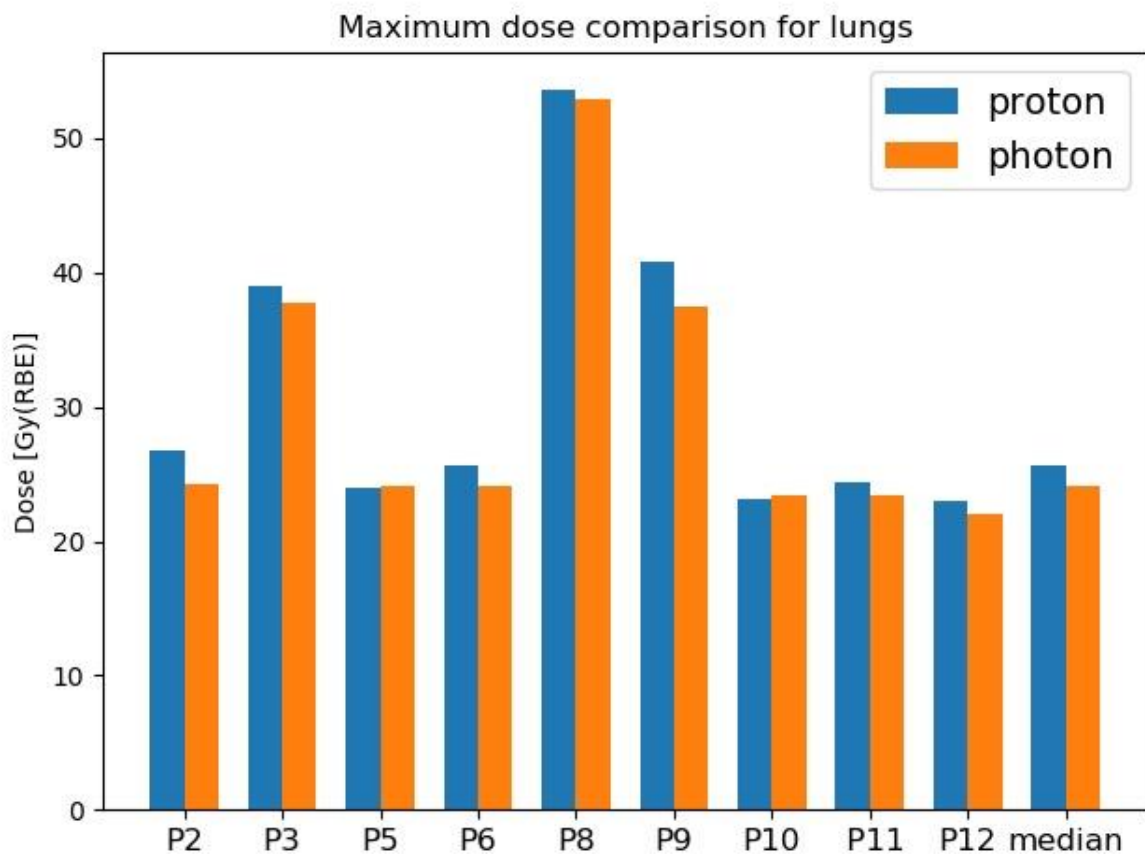
Figure 5.4. Maximum dose comparison of photons and protons comparison for lungs. The median maximum doses are displayed in the last bars.

NTCP comparison

As table B.1. and figure 5.5 and 5.6. show, among 6 of medulloblastoma patients, the NTCP is decreased by a factor 2 and more by protons for 5 patients; even for one medulloblastoma patient(P9) NTCP is decreased by a factor of 4.7, from 0.0265 to 0.0056, by using protons. For one medulloblastoma patient(P10) the NTCP value is produced by photon and proton is the same. Of 3 neuroblastoma patients proton reduced the NTCP value by a factor of 2.3 or more for 2 patients (p11 and P12). For one Ewing sarcoma patient the proton influence is the same as neuroblastoma patient. For one neuroblastoma, wing sarcoma and RMS patients the NTCP values are not included since the mean dose and therefore NTCP of those patients is insignificant. Generally, Proton's NTCP value is much smaller than the photon's for all type of pediatric malignancies patients and this confirm that protons, for the endpoint of radiation pneumonitis are more near to achieve the aim of radiotherapy i.e. achieving high probability of TCP with low risk of NTCP.
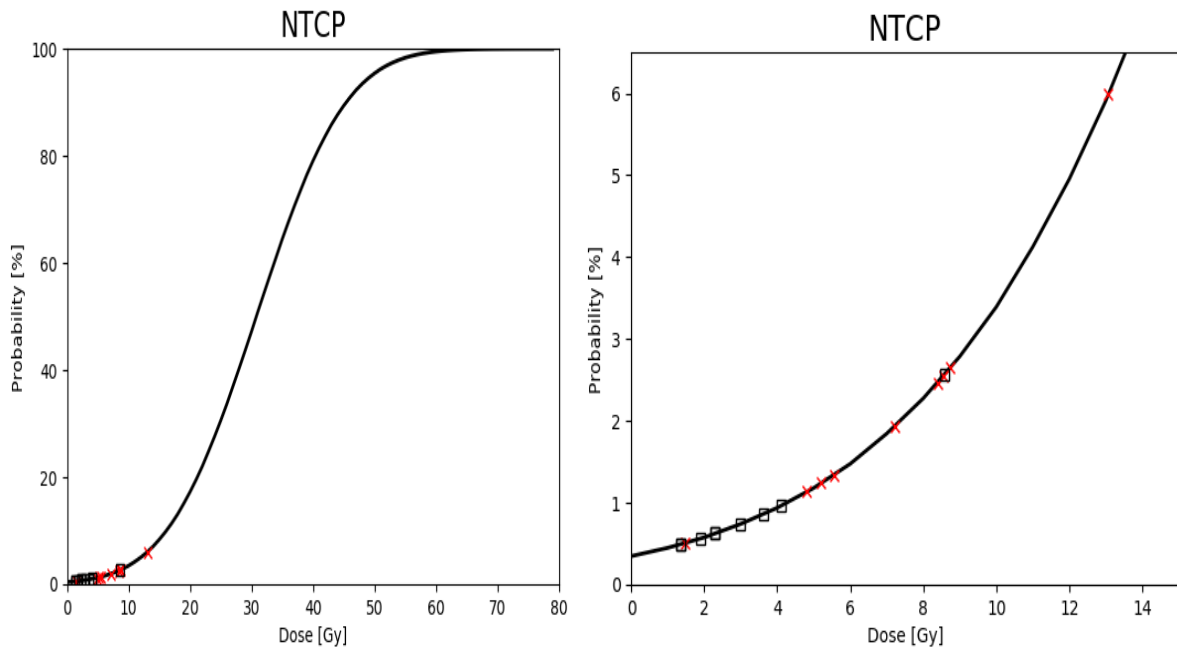
Figure 5.5. The plot that shows the NTCP model and compare the NTCP values (the probability of radiation pneumonitis) from protons(box) and photons(red). The probability of the patients to face radiation pneumonitis is less than 6% for all patients. The highest value is produced by photon whereas the highest probability of having radiation pneumonitis estimated from proton plan is 2.6%.

N.B. Red and rectangle represent photons and protons respectively.
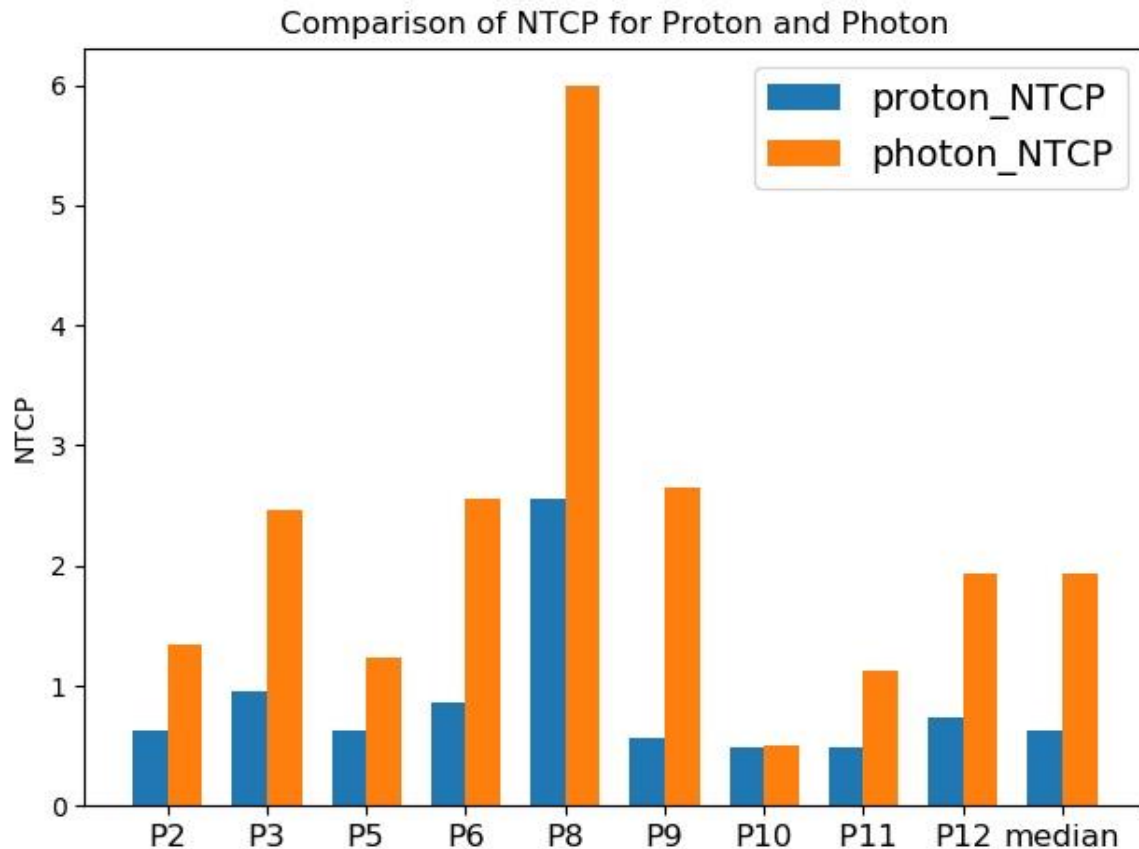
Figure 5.6. Bar graph that show lung NTCP in % for the endpoint of radiation pneumonitis produced by photon and proton. The median of NTCP values are displayed in the last bars.

5.2 Heart Dose.

DVH metrices

The dose to heart were overall lower from protons compared to photons (Figure5.9). As seen in the DVHs, protons gave little dose to parts of heart while for the photon plans, the heart dose varied more between the different patients.

As table A2. shows the dose metrices V_{15} from protons for four medulloblastoma patients is less than from photons treatment techniques except for one patient (P9). For this patient, V_{15} is equal to zero from both treatment techniques. The dose constraints

for heart, V_{25} is equal to zero from both treatment techniques for all four medulloblastoma patients. The dose constraints for heart, V_{25} should less than 10% [35]. For one Ewing sarcoma patient the value of V_{15} is decreased by a factor of 9 by protons compared to photons. For this particular patient the value of V_{25} is different from zero for both treatment techniques but those values, 0.036% and 0.425% for protons and photons treatment techniques respectively is much smaller than the dose constraints value of heart(V_{25}=10%); therefore, the patient can-not expect long term cardiac mortality and likely or no clinical gain is achieved for the patient by using protons instead of photons.

V_{15} of neuroblastoma patients has similarity with Ewing sarcoma and medulloblastoma patients i.e. V_{15} of protons is much less than photon treatment techniques. For one Neuroblastoma patient (P12) proton reduced V_{15} from 10.54% to 1.33% compared to the photons treatment.

For the RMS both dose metrices V_{15} and V_{25} are zero because the amount dose that was delivered by both treatment techniques were small. Two medulloblastoma, one Ewing sarcoma and one neuroblastoma patients' DVH metrices are not calculated because the dose to heart for those patients are insignificant.
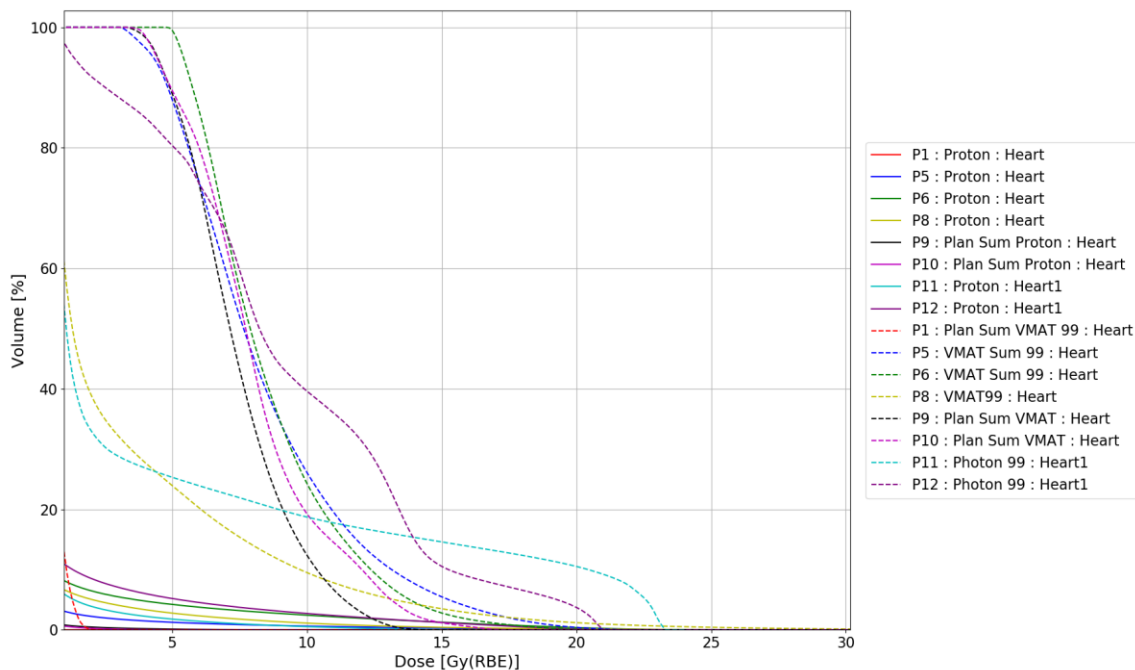
Figure. 5.7. Dose Volume histogram for the heart for proton plans (solid lines) and photon plans (dashed lines).

Mean dose.

Over all Figure 5.8 below illustrate the photons doses to the heart are consistently higher than proton doses. According to the bar graph, the mean dose of protons for all pediatric patients is less than 0.8Gy whereas the mean dose from photons to 7 to 8 of patients greater than 3.5Gy i.e. only one patient received a mean dose which is less than 3.5Gy. The mean dose values for two medulloblastoma (P2 and P3), one Ewing sarcoma (P4) and one neuroblastoma (P7) patients are insignificant and therefore not included.

As we see from the bar graph, the value of mean separating the higher half from lower half of the dose, median of the mean proton is 0.24Gy and photon's is 7.8Gy.
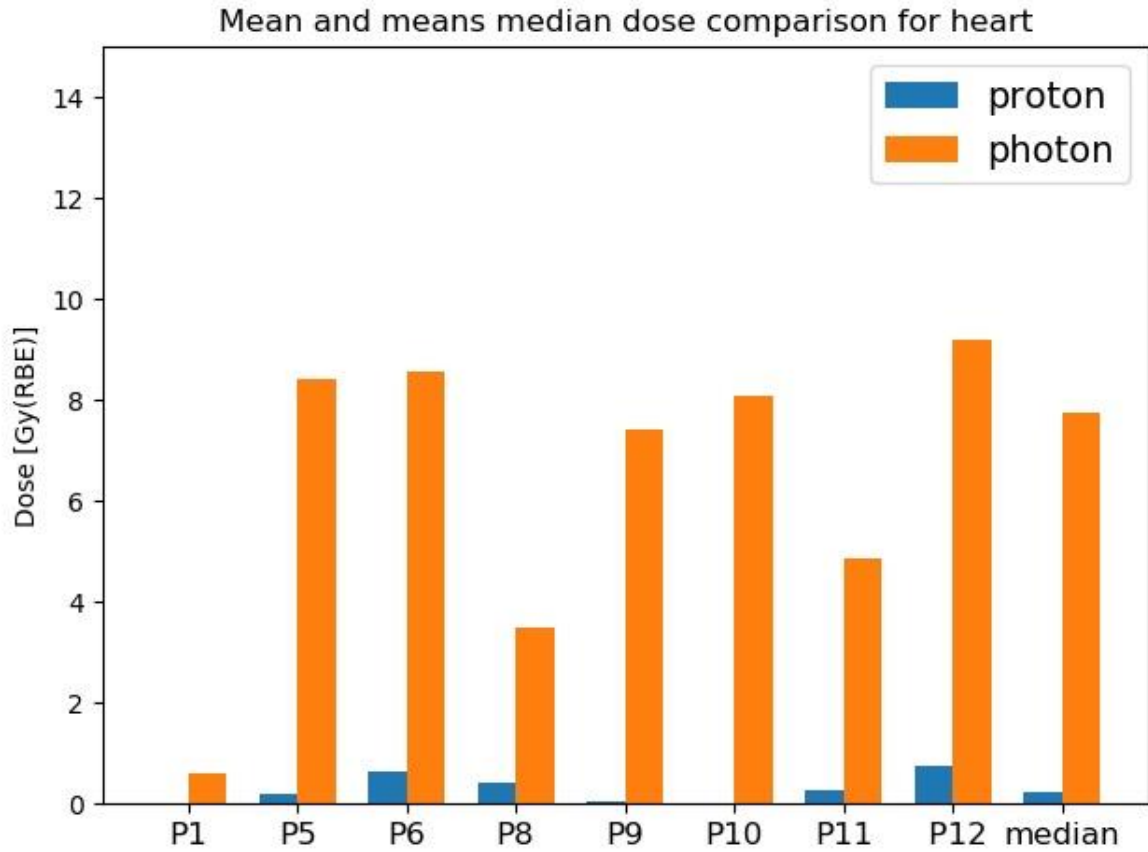
Figure 5.8. Comparison of mean dose of proton and photon for the heart. The median mean doses are displayed in the last bars.

Maximum dose.

As table D.1 shows among 8 pediatric malignancies patients the maximum dose which was delivered by photon to 7 patients is much larger than proton delivery but the maximum dose of one medulloblastoma patient (P6) that was delivered by photon is smaller than protons. The values of maximum dose for one Ewing sarcoma(P4) and neuroblastoma(P7) patients and for two medulloblastoma patients (P2 and P3) are insignificant.
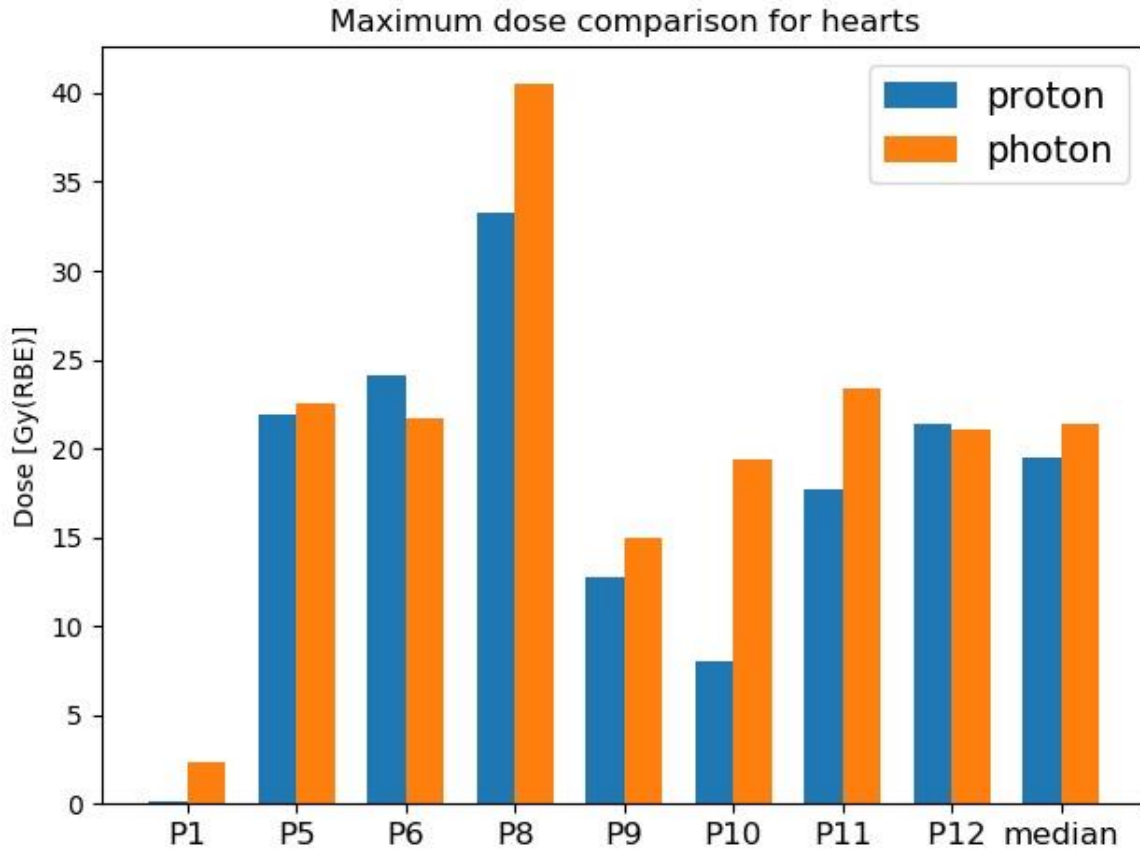
Figure 5.9. Maximum dose comparison of photons and protons comparison for hearts. The median maximum doses are displayed in the last bars.

Relative risk of cardiac mortality.

As seen in figure 5.10 relative risk of cardiac mortality that is produced by photon is greater than the value that is produced by proton. The result further summarized in table B.2. The value of relative risk of cardiac mortality that is produced by proton is less than 1.5 whereas the value that is produced by photon is almost greater than 3 except for one RMS patient whose value is 1.357. The ratios, RR_{pr}/RR_{ph} that was calculated by using equation (6) show that all values less than or equal 0.4 except for RMS patient. The ratio and individual values of relative risk of cardiac mortality shows that, according to the applied risk model, delivery of photon increases the probability of the patients to face cardiac mortality by more than a factor of two compared to proton.

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Photon's relative cardiac mortality values for medulloblastoma patients higher than the other patients. This indicate that, the medulloblastoma patients have a larger probability to face cardiac mortality than the other patients. Similarly, Proton's neuroblastoma relative cardiac mortality values are larger than the other patients.
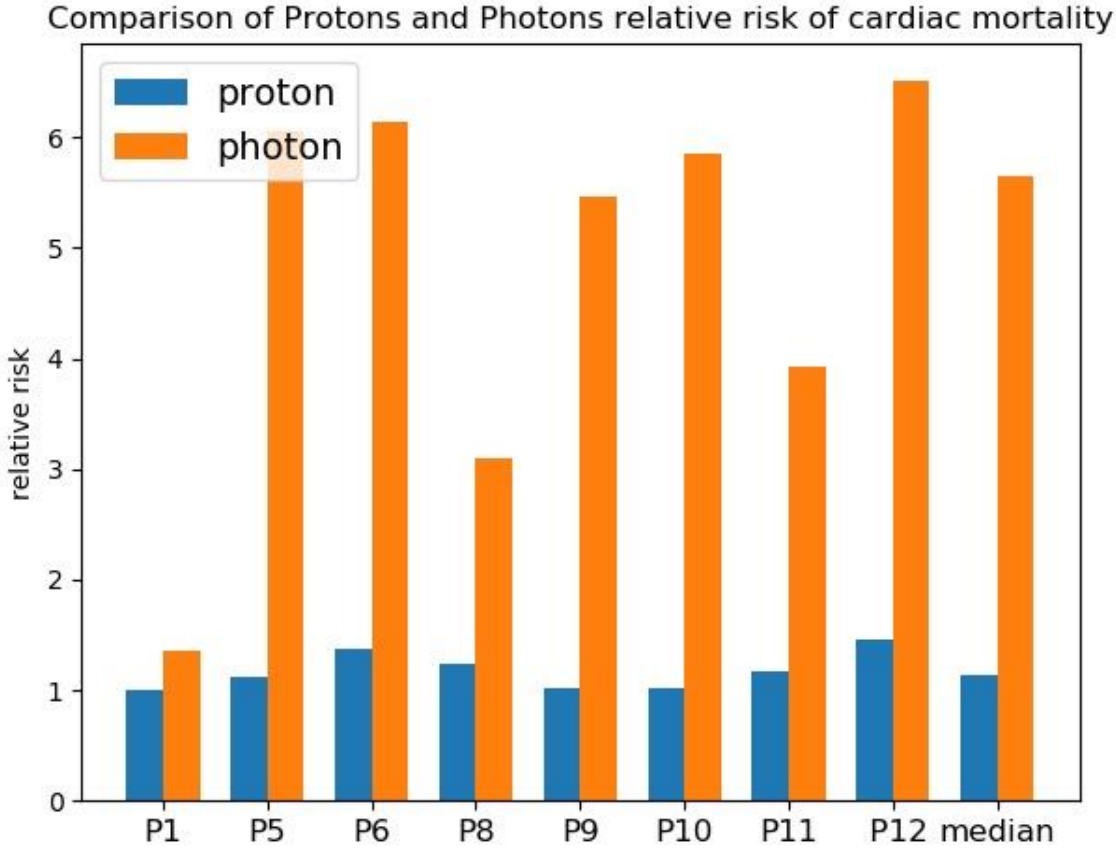
Figure 5.10 the relative risk of cardiac mortality comparison.

5.3 Doses for other OARs

Dose for Lungs and hearts were discussed in detail but several other OARs were also delivered significant doses for all pediatric cancer patients. The results of those OARs were discussed by classifying the organs such as abdominal organ, CNS organs, sense organs, thoracic cavity organs except heart and lung based on mean, median and maximum dose.

The mean and median doses of photon that was delivered for abdominal organ such as stomach, liver, bladder, bowel (large and small) and rectum were larger than the same types of doses that was delivered by proton treatment techniques. Referring maximum doses which were delivered by both treatment techniques for those organs is variable; meaning for certain organs like rectum and bladder protons deliver excess maximum doses as shown in table D.1.

Referring CNS organs like brain, cerebellum, hypothalamus and cerebrum, the mean, median and maximum doses that was delivered by protons larger than the doses that was delivered by photons treatment techniques for majority of pediatric cancer patients except the Spinal cord where mean and median dose from photon are dominant. Especially, for medulloblastoma patients the value of the doses, mean, median and maximum doses for OARs are high, this because of parts of Central nervous are considered as a secondary target as they found near to PTV and for allowing uniform dose distribution across the OARs.

When parts of sense organs like cochlea (right and left) and retina (right and left), lacrimal gland (right and left) and lens (right and left) are considered, the mean, median and maximum doses that was delivered to parts of ear from photon is larger than protons whereas the doses to the parts of eye from proton is larger (table D.1).

Organs located at thoracic cavity such as breast, thyroid gland and Oesophagus were delivered smaller dose by protons than photons for mean, median and maximum doses as shown in table D.1.

The mean, median and maximum dose to kidneys (left and right) from photon treatment techniques is larger than proton's dose for majority of malignancies patients.

Even if, the dominancy of photon and proton interchanges for different dose values in retina (left) as shown in figure 5.11. for different pediatric cancer patients, the mean and the maximum doses which were delivered for retina (left) of the different

malignancies patient by proton is overall larger than photon (see figure 5.12. and figure 5.13)
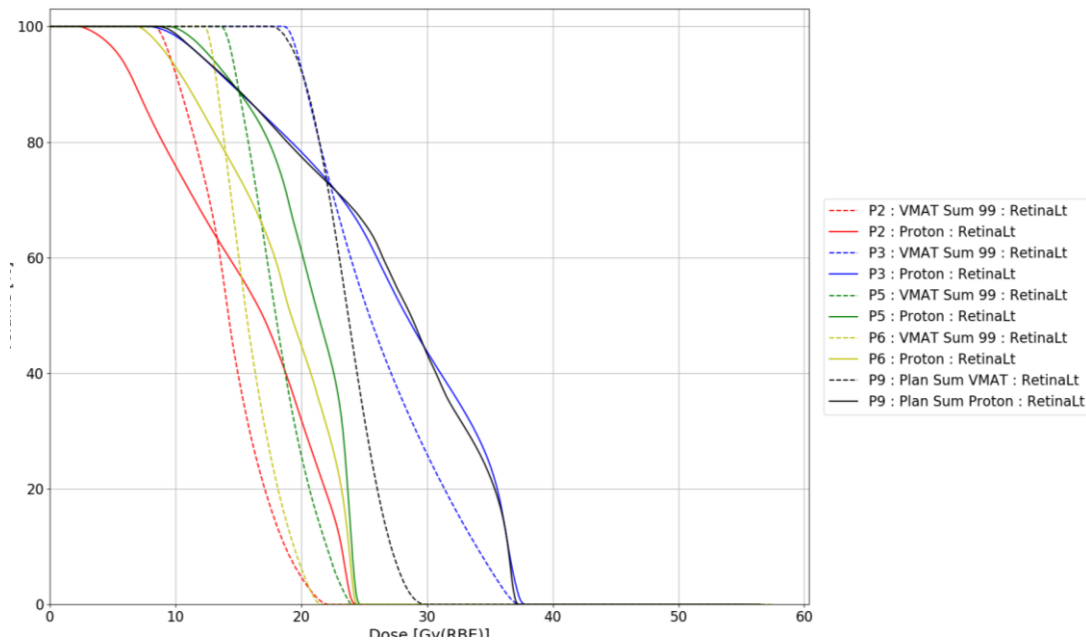
figure 5.11 A plot that shows the dose for retina (left) by protons (solid lines) and photons (dashed lines).
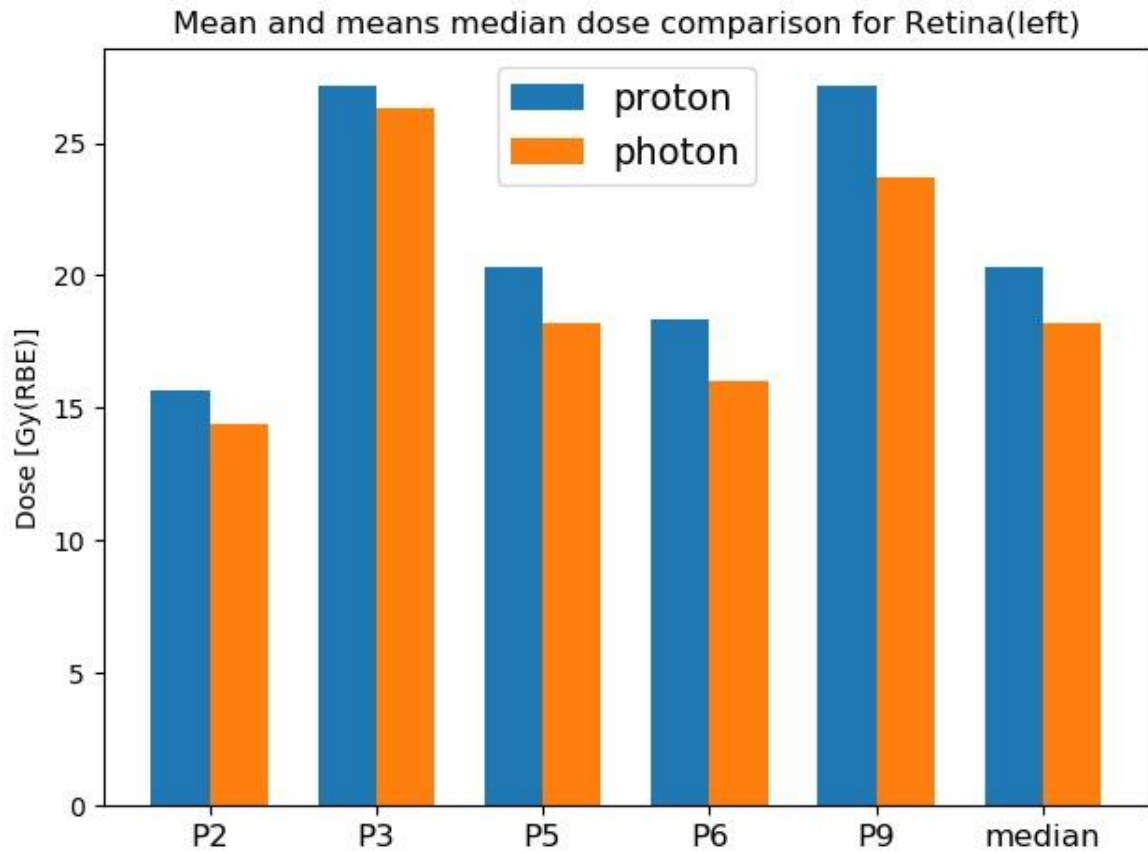
figure.5.12 Comparison of mean dose of proton and photon to retina (left) for medulloblastoma patients. The median mean doses are displayed in the last bars.
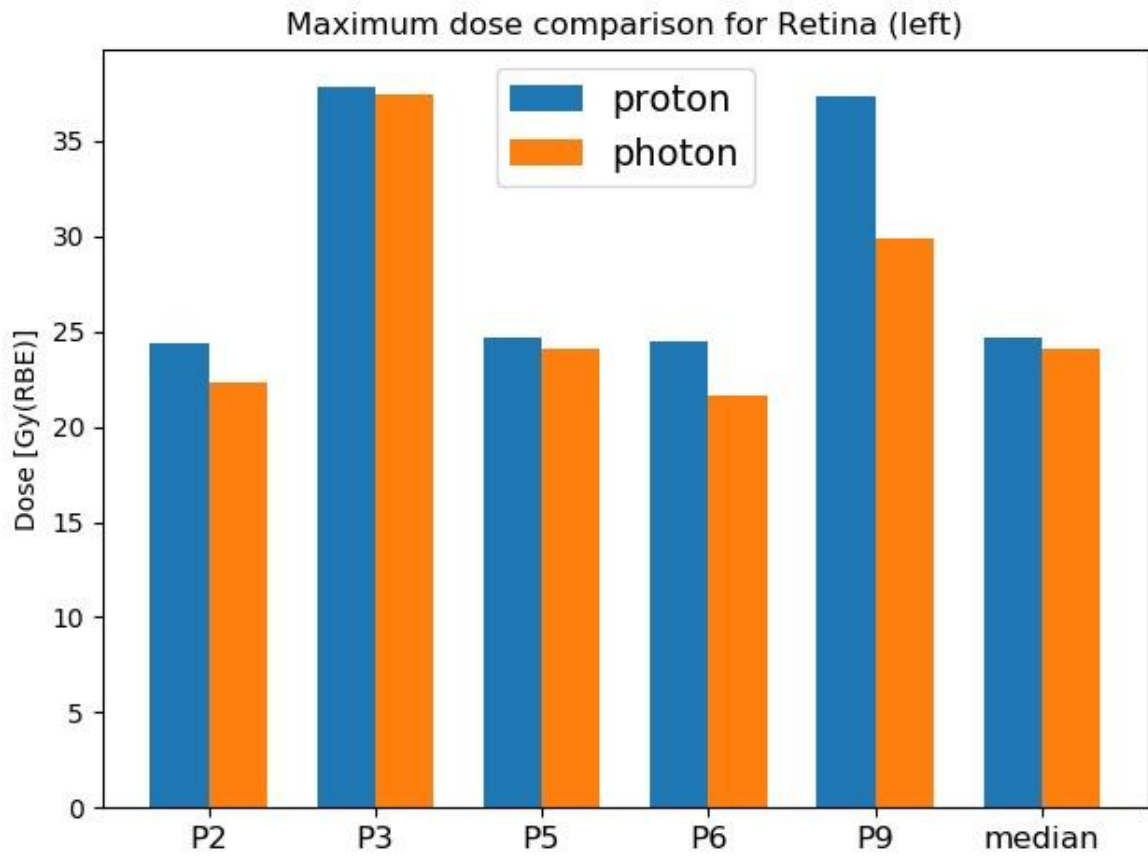
Figure 5.13 Comparison of maximum dose of proton and photon to retina(left) for medulloblastoma patients. The median mean doses are displayed in the last bars.

For esophagus, the doses varied significantly between the patient, but in general, protons is shown to give some dosimetric advantage also for this OAR. However, both treatments delivered relatively high dose to one Ewing sarcoma patient 's esophagus (P8) as shown in figures 5.14, 5.15 and 5.16.
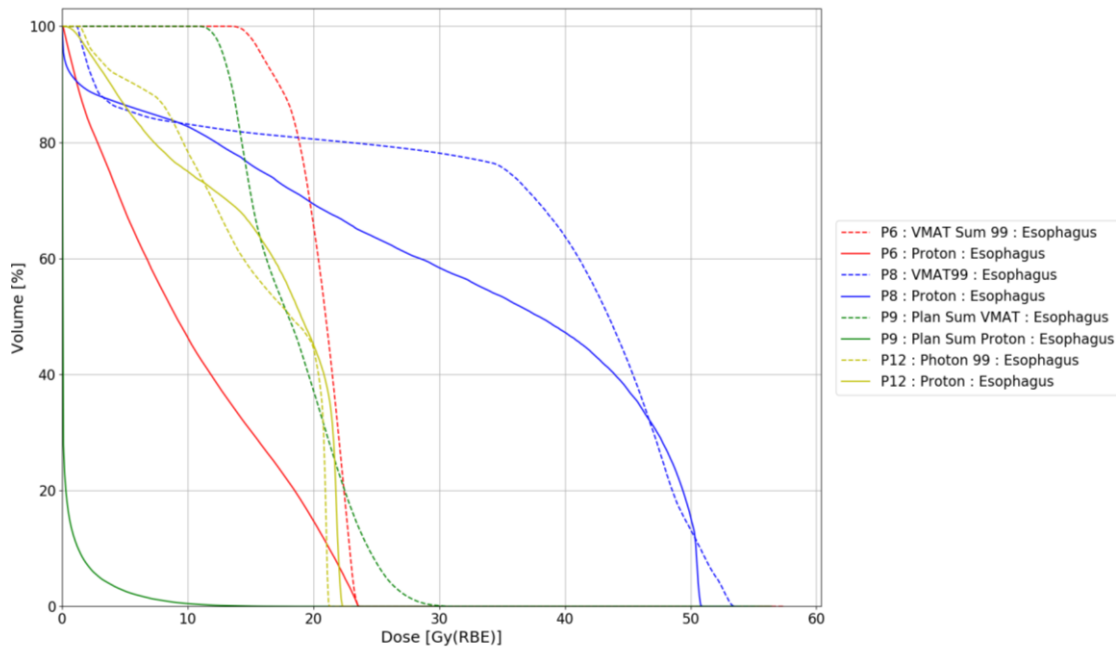
Figure 5.14. A plot that shows the dose to the esophagus by proton and photon with their corresponding treatments plan.
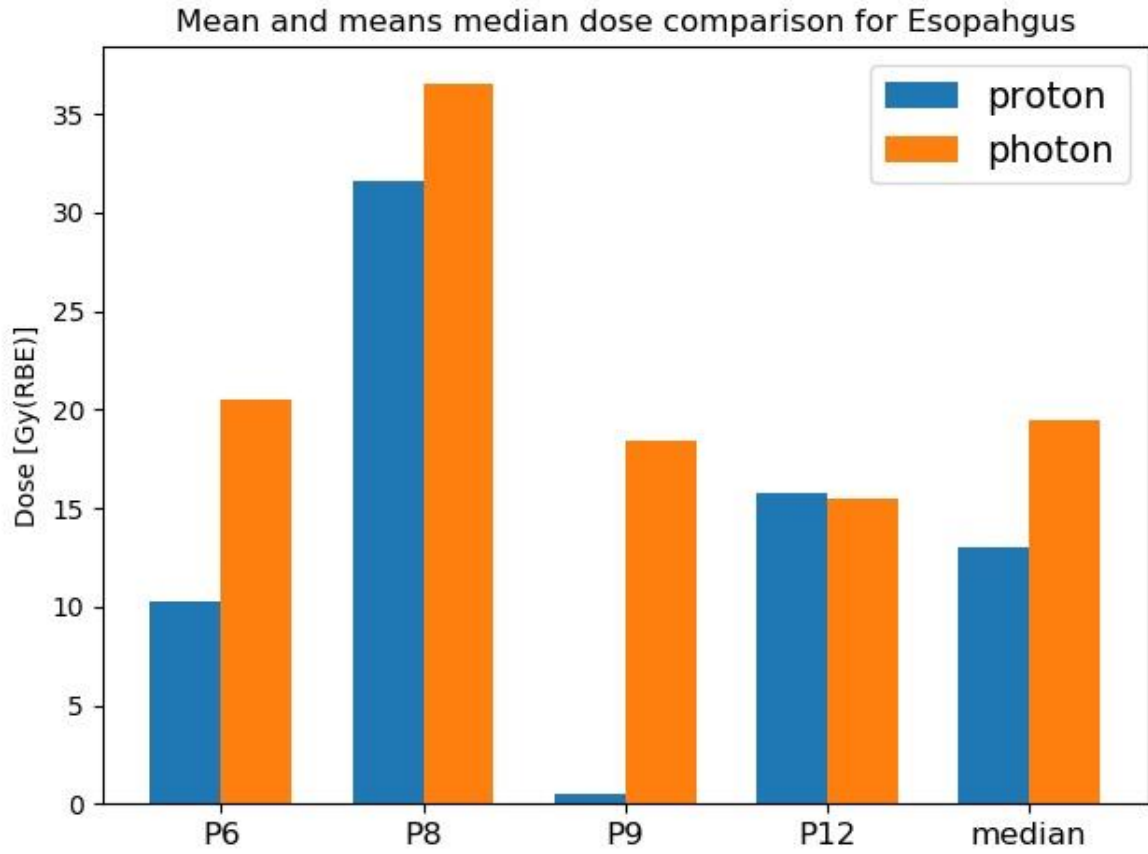
Figure 5.15 Comparison of mean dose of proton and photon to the esopahgus. The median mean doses are displayed in the last bars.
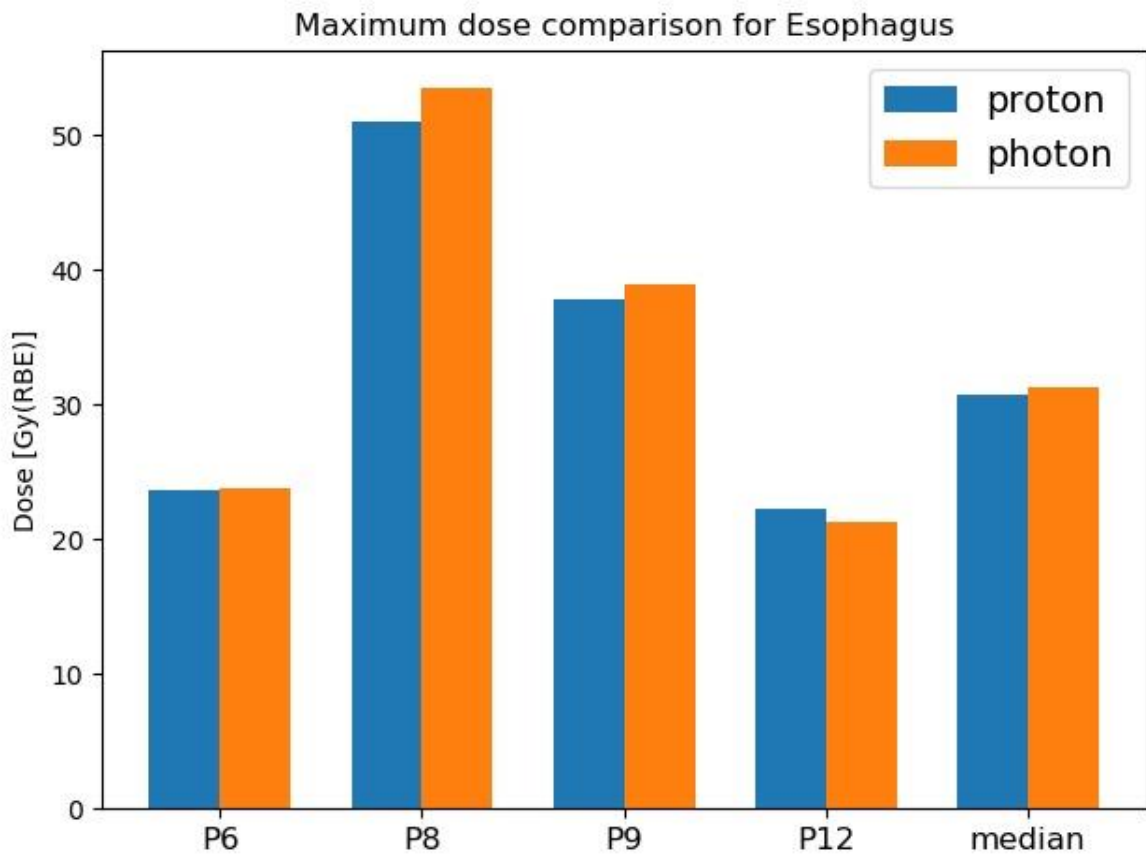
Figure 5.16 Comparison of maximum dose of proton and photon to the esophagus. The median mean doses are displayed in the last bars.

6. Discussion

6.1 Dosimeric and DVH metrics aspects.

This study was conducted in order to compare the doses to OARs from proton and photon therapy for different pediatric cancer patients with radiotherapy to the thorax, abdomen and pelvis. In addition, to estimate and compare late morbidity based on two organ at risks, heart and lung. Mean, median, maximum dose, different DVH metrices and NTCP are useful parameters to evaluate the aim of RT which is to treat patients according to well defined risk groups in order to maximize cure rates and side effects in survivor [10]. Even if delivering low doses for OAR can-not guarantee the normal tissues not having late effects, all included types of cancer OAR especially lungs and heart received a lower amount of dose from protons than photons. For example, one medulloblastoma patient's lungs (P9) received 9.4 Gy and 1.89 Gy of mean dose from photon and proton respectively. Particularly, the amount of different doses (mean, median and maximum dose) that was received by heart from protons was too small. One medulloblastoma patients' heart received 0.03Gy and 7.4Gy of mean dose from proton and photon treatment techniques respectively. Similarly, even if the amount of dose which was delivered by both treatment techniques to the heart was very small, the hearts of all types of malignancies received an even smaller amount of doses (mean, median dose and maximum dose) from protons than photons. This result, the dominancy of protons over photons by delivering small amount mean and median doses agree with other different case studies[36, 37]. For the lungs the result that was found based on DVH metrices were slightly different from the comparison of the two treatment techniques based on doses. The lower dose-metrices like D_2 and D_{40} show that protons are better than photons but the higher dose- metrices like V_{15}, V_{18}, and V_5 show that photon is better than protons. This confirms and agree with the advantage of proton beams over photon beams (IMRT) become apparent in the medium and low - dose range (i.e. <50% of prescription isodose), where the superior over all dose-volume characteristics of proton lead to a significantly improved OAR sparing[38]. The

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volume metric V_{20} and V_5 are dose constraints for lung; meaning, dose constraints are parameters that can used to estimate the endpoints (i.e. late effects) post treatment or tolerance limit of the normal tissue. Based on the results of the dose constraint analysis, the patient will not experience radiation pneumonitis since the value of V_{20} is less than 35% and V_5 is less than 65%, for both treatment techniques. Results for heart has a difference from the lung's DVH metrices; DVH metrices for lung show that for low dose protons were better than photons but for high doses the opposite was true. DVH metrices for heart confirmed that for high dose and low doses, proton spares the heart than photon. The dose constraints for heart, V_{25} is zero for both treatment techniques except for one Ewing sarcoma patient. The values were, 0.036% and 0.43% for Ewing sarcoma patient from protons and photons. This is much smaller than 10% which is the tolerance limit of heart and beyond this value the patient may experience cardiac toxicity but as the values from the patient shows that the patient has minimum probability to experience cardiac toxicity. The value of lower dose metrices like V_{25} is zero for most patients, this may happen because of the low amount of dose is delivered for the organ by both treatment techniques.

6.2 Radiation Pneumonitis based on NTCP and cardiac mortality.

As table B.1 shows that all values of NTCP which is produced by photon is larger than protons and the difference between photon's and Proton's NTCP is negative. Even if the lowest value of NTCP that is produced by proton and photon treatment techniques for medulloblastoma patients are equal, the highest value that is produced by photon is almost 2.5 times the highest value of Proton's NTCP for these patients, this clearly shows that the organ, lung of medulloblastoma patients is spared by protons. Despite of the value of NTCP which was produced by protons for Ewing sarcoma (P8) patient is third highest of all NTCP values, this value is much less than NTCP value that was produced by the photon treatment technique. As medulloblastoma and Ewing sarcoma patients, the lung of neuroblastoma patients was spared by protons.

NTCP estimates the risk by modelling of a given side effects as a function of increasing dose to organ at risk/ probability of a given side effects as a function of increasing dose to the organ at risk (OAR) or increasing volume with an OAR receiving a certain dose[37]; therefore, the relationship between MLD and the risk of RP is described by NTCP modelling like the LKB model which is used for in this work. According to the results based on the LKB model, the values of the NTCP which is produced by photons is larger than Proton's. This indicate that probability of having RP is also increased more by photons than from protons. Even if photons increase inducing radiation pneumonitis, the probability of all patients to have RP is very low since the value is less than or equal 2.56% for all patients.

The relative risk of cardiac mortality is depends on the mean dose of the heart but cardiac mortality can-not be estimated by LKB model since the risk of radiation induced valvular disease can-not be dependent only on heart dose distribution[33]. However, according to the model used in this thesis radiation induced valvular disease only depend on heart dose distribution. Therefore, the radiation induced cardiac mortality was compared the ratio of the relative risk which between protons to photons. The last column of table B.2 show that the ratio is less than one. This implies that proton has a lower probability to induce valvular disease than photons.

7. Conclusion.

The values of mean, median and maximum doses show that by using proton treatment techniques the delivery of doses is smaller than for photon treatment techniques. Most OARs were spared by protons such as breast, esopaghus and Spinal cord but few OARs such as (Left and right retina), hypothalamus and lens were spared by photons compared to Protons treatment. Referring to DVH metrices for the lungs, photons is slightly better than protons for high dose region whereas protons are better than photons at low doses. For the heart, as different doses such as mean, median, maximum and DVH metrices show that proton clearly spared the heart compared to photons. Besides, photons gave a higher risk of radiation pneumonitis and cardiac mortality than protons. However, the values of doses from both photon and proton are much far less than the value of the dose tolerance limits of both organs therefore, the probability of the patients to experience late effects is still quite low, also for photons. Overall, this thesis shows that protons give several dosimetric advantages. However, in many cases it may be difficult to observe improved clinical outcome as the risk for radiation pneumonitis and cardiac mortality was relatively low for both proton and photon treatments

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Appendix A

DVH metrices for lung and hearts.

Table.A.1: DVH metrics of lung dose for proton and photon treatment plan.

Patient type and patients	Proton plan's dosimetric values		Photon plan's dosimetric values	
Medulloblastoma	$D_{40}[Gy]$	$V_y[cc]$	$D_{40}[Gy]$	$V_y[cc]$
P2	0.08	$V_{15}=108.41$	4.99	$V_{15}=99.44$
P3	0.08	$V_{18.5}=240.24$	8.139	$V_{18.5}=232.58$
P5	0.08	$V_{15}=42.00$	4.80	$V_{15}=31.70$
P6	0.91	$V_{18}=94.678$	8.44	$V_{18}=86.078$
P9	0.07	$V_{20.6}=81.54$	8.78	$V_{20.6}=81.31$
Neuroblastoma	$D_{40}[Gy]$	$V_y[cc]$	$D_{40}[Gy]$	$V_y[cc]$
P11	0.07	$V_5=36.12$	0.61	$V_5=22.79$
P12	0.25	$V_{21.5}=24.97$	5.33	$V_{21.5}=11.21$
Ewing sarcoma	$D_{40}[Gy]$	$V_y[cc]$	$D_{40}[Gy]$	$V_y[cc]$
P8	0.6	$V_{28}=58.82$	13.64	$V_{28}=57.28$

Table.A.2 DVH metrics of heart for proton and photon treatment plan
N.B. V_y% / [cc] shows that the desired volume specified percent per absolute units(cc).

Patient type and patients	Proton plan's dosimetric values		Photon plan's dosimetric values	
Medulloblastoma	D_2[Gy]	V_y% / [cc]	D2[Gy]	V_y% /[cc]
P5	2.46	V_{15}=0.28/0.74 V_{25}=0	17.49	V_{15}=5.48/14.33 V_{25}=0
P6	11.667	V_{15}=1.26/2.90 V_{25}=0	15.72	V_{15}=2.79/6.41 V_{25}=0
P9	0.148	V_{15}=0 V_{25}=0	12.37	V_{15}=0 V_{25}=0
P10	0.176	$V1_5$=0 V_{25}=0	14.24	V_{15}=1.16/7.43 V_{25}=0
RMS	D_2[Gy]	V_y% / [cc]	D2[Gy]	V_y% /[cc]
P1	0.011	V_{15}=0 V_{25}=0	2.33	V_{15}=0 V_{25}=0
Neuroblastoma	D_2[Gy]	V_y% /[cc]	D_2[Gy]	V_y% /[cc]

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P11	4.492	V_{15}=0.06/0.11 V_{25}=0	23.00	V_{15}=14.59/25.55 V_{25}=0
P12	12.20	V_{15}=1.33/1.33 V_{25}=0	20.56	V_{15}=10.54/11.42 V_{25}=0
Ewing sarcoma	D_2[Gy]	V_y % / [cc]	D_2[Gy]	V_y % / [cc]
P8	6.84	V_{15}=0.42/0.45 V_{25}=0.036/0.039	17.62	V_{15}=3.502/3.772 V_{25}=0.425/0.458

Appendix B

Table B.1. NTCP comparison of proton and photon.

N.B. Proton$_{MLD}$ and photon$_{MLD}$ are the value of mean lung dose by proton and photon respectively. Proton$_{NTCP}$ and Photon$_{NTCP}$ are the values NTCP produced by proton and photon. The last column shows the difference of fourth and fifth column.

Patient	proton$_{MLD}$	photon$_{MLD}$	Proton$_{NTCP}$	Photon$_{NTCP}$	Proton$_{NTCP}$-photon$_{NTCP}$
P2	2.286	5.565	0.0062	0.0134	-0.0072
P3	4.105	8.4	0.0096	0.0246	-0.015
P5	2.297	5.208	0.0062	0.0124	-0.0062
P6	3.631	8.567	0.0086	0.0255	-0.0169
P8	8.577	13.074	0.0256	0.06	-0.0344
P9	1.889	8.75	0.0056	0.0265	-0.0209
P10	1.364	1.463	0.0049	0.0050	-0.0001
P11	1.363	4.815	0.0049	0.0113	-0.0064
P12	2.992	7.225	0.0073	0.0193	-0.012

Table B.2 the values of relative risk of cardiac mortality of each patients for both protons and photons with their corresponding protons and photons with their corresponding ratio.

Patients	R_{pr}	R_{ph}	R_{pr} / R_{ph}
P1	1.002	1.357	0.7378
P5	1.118	6.045	0.185
P6	1.379	6.138	0.2246
P8	1.242	3.1	0.4008
P9	1.019	5.454	0.1868
P10	1.014	5.845	0.1734
P11	1.169	3.924	0.2980
P12	1.452	6.515	0.2228

Appendix C

C.1. Patients data who were treated from different malignancies and with their corresponding treatment period.

Patient name	Types of malignancies	Years of treatment
P1	RMS	2014
P2	Medulloblastoma	2014
P3	Medulloblastoma	2014
P4	Ewing sarcoma	2015
P5	Medulloblastoma	2015
P6	Medulloblastoma	2015
P7	Neuroblastoma	2015
P8	Ewing sarcoma	2016
P9	Medulloblastoma	2015
P10	Medulloblastoma	2015
P11	Neuroblastoma	2015
P12	Neuroblastoma	2015

C.2. The total dose which was delivered for patients by two treatment techniques and the number of fields that was used by photon plan.

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Patients	Apparatus	Number of fields for VMAT	Proton plan	Photon plan	Total Dose (Gy).
P1	Varian true beam STX	2+1	Proton	Plan sum VMAT 99	50.4
P2	Varian true beam STX	8+2	Proton	VMAT sum 99	54
P3	Elektra synergy and Varian true beam STX	6+1	Proton	VMAT sum 99	54
P4	Varian true beam STX	2	Proton	VMAT 99	54
P5	Varian true beam STX	6+2	Proton	VMAT sum 99	54
P6	Elektra synergy and Varian true beam STX	6+2	Proton	VMAT sum 99	54
P7	Varian true beam STX	4	Proton	VMAT 99	21

P8	Varian true beam STX	4	Proton	VMAT 99	50.4
P9			Plan sum proton	Plan sum VMAT	54
P10			Plan sum proton	Plan sum VMAT	54
P11			Proton	Photon 99	21
P12			Proton	Photon 99	21

Appendix D

D.1. Different types of doses, Mean, Median, and Maximum values that were delivered for different pediatric malignancies patients by proton and photon treatment techniques.

N.B. P1 to P12 represents the patient's number and Prmed=proton's median which the median dose that was delivered by proton treatment techniques. Similar analogous is used for other abbreviation also.

Prmea= proton's mean, Phmed=photon's median, phmea= photon's mean, prmax=proton's maximum, phmax=photon's maximum.

 (phmed-prmed), (phmea-prmea) and (phmax-prmax) is the difference of type of doses which were delivered by photon and proton treatment techniques.

patient P1								
OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bladder	42.14	42.13	41.50	41.55	42.86	42.74	-0.64	-0.57	-0.11
Bowel space	0.39	14.24	22.12	25.91	52.14	52.89	21.73	11.67	0.75
bowel large	6.61	0.00	19.17	21.04	51.47	51.69	12.56	21.04	0.22
bowel small	5.33	17.08	25.76	29.13	51.81	52.78	20.43	12.05	0.97
fermur left	0.00	2.83	16.28	16.31	36.37	30.17	16.27	13.48	-6.20
fermur right	0.00	0.23	15.75	15.86	16.03	23.14	15.75	15.63	7.11
Growth plate left	3.66	6.04	19.64	19.70	28.77	24.91	15.98	13.66	-3.86
growth plate right	0.01	0.45	15.47	15.72	7.80	21.03	15.46	15.26	13.22
heart	0.00	0.00	0.49	0.60	0.11	2.33	0.49	0.59	2.22
kidneyLt	1.52	10.55	5.57	8.66	45.72	49.09	4.06	-1.89	3.37
kidney rt	4.80	10.00	6.77	8.58	43.51	36.01	1.98	-1.43	-7.49
liver	0.00	1.08	6.22	8.79	42.55	42.32	6.21	7.71	-0.23
nerve roots	24.78	24.49	13.85	14.38	39.14	24.24	-10.93	-10.12	-14.90
rectum	22.95	25.13	20.24	24.65	42.75	42.69	-2.71	-0.49	-0.06
skin	0.00	2.28	7.77	7.85	42.32	41.31	7.77	5.57	-1.01
spainal cord	40.29	31.69	26.50	20.93	49.38	35.41	-13.79	-10.76	-13.97
stomach	0.00	3.62	18.77	19.54	50.65	50.32	18.76	15.92	-0.34
Zpevlvic vessel	42.40	44.25	41.95	43.71	52.14	52.14	-0.45	-0.54	0.00
Zaorta	49.03	47.14	49.83	47.11	51.57	52.01	0.80	-0.03	0.43
Zpost chemonode	51.16	51.17	51.00	51.00	51.74	52.08	-0.16	-0.16	0.34
Zpara-aortic	49.44	47.30	49.86	47.18	51.03	52.01	0.42	-0.13	0.98
z_softtissues	39.85	31.30	35.25	30.18	51.84	52.87	-4.60	-1.12	1.03

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bones	23.39	23.11	23.96	24.04	56.21	54.57	0.57	0.93	-1.64
brain	24.84	29.18	24.54	30.00	5.22	56.93	-0.29	0.81	51.71
brainSupra tent	24.61	26.34	24.40	26.78	55.79	56.37	-0.21	0.44	0.58
brain stem	49.45	44.49	52.37	49.02	55.58	56.93	2.92	4.52	1.34
brainstemCore	48.87	45.21	51.91	49.52	55.34	56.91	3.03	4.32	1.57
brain stemsurface	50.62	43.77	53.25	48.58	55.59	56.93	2.63	4.81	1.34
cerebellum	57.62	48.08	53.52	50.14	56.22	56.89	-4.11	2.06	0.67
clip box	23.34	22.69	23.78	23.01	36.80	31.41	0.44	0.32	-5.38
cochlea LT	24.36	24.37	36.78	36.80	24.98	37.65	12.43	12.43	12.68
cochlea Rt	24.41	24.42	37.91	37.92	24.70	38.80	13.50	13.50	14.10
cord	23.42	23.57	24.01	24.25	47.92	45.97	0.58	0.67	-1.96
cribriform	24.51	24.53	24.48	24.47	25.05	25.16	-0.02	-0.06	0.11
Hippo head Lt	25.53	26.13	35.35	35.27	32.60	40.47	9.81	9.14	7.88
hippohead Rt	25.07	25.40	34.84	34.79	29.48	38.92	9.77	9.39	9.44
hippo Lt	28.51	29.79	35.11	34.79	43.19	45.79	6.60	5.00	2.60
hippoRt			34.18	33.62	37.82	39.84	34.18	33.62	2.02
Hippo Tail Lt	33.64	33.70	34.24	34.29	43.19	45.58	0.60	0.60	2.39
hippo tai Rt	32.51	31.97	32.41	32.33	37.82	39.84	-0.09	0.35	2.02
hippocampusIL	28.51	29.79	35.11	34.79	43.19	45.58	6.60	5.00	2.39
hypothalamus	25.00	26.05	25.72	26.05	38.90	31.54	0.71	0.00	-7.36
kidneyLt	0.00	2.22	6.19	7.66	23.42	23.00	6.19	5.44	-0.42
kidney rt	0.14	3.57	8.01	8.76	23.53	23.92	7.88	5.20	0.38
lacrimal Lt	22.30	18.95	18.07	17.93	23.13	22.09	-4.23	-1.02	-1.04
lacrimal Rt	22.91	20.86	17.79	17.99	23.40	23.81	-5.12	-2.87	0.41
lensRt	14.32	14.19	9.10	9.12	18.99	10.74	-5.22	-5.07	-8.25
lensLt	11.82	12.43	9.39	9.45	19.76	10.75	-2.43	-2.99	-9.00
lung Lt	0.00	1.92	3.39	5.12	25.32	24.25	3.39	3.20	-1.08
lung Rt	0.00	2.62	4.04	5.96	26.71	24.30	4.03	3.35	-2.40
lungs	0.00	2.29	3.73	5.57	26.71	24.46	3.72	3.28	-2.25
optichaism	0.00	0.00	26.58	26.55	0.00	26.93	26.58	26.55	26.93
optic nervLt	24.51	24.49	24.87	24.44	24.97	28.42	0.36	-0.05	3.46
optic nerveRt	24.40	24.41	24.18	23.99	24.94	28.13	-0.23	-0.43	3.20
parotid_L_cagr	18.40	17.53	21.73	20.87	24.34	31.41	3.34	3.34	7.06
parotid_R_cagr	22.33	20.04	22.32	21.84	24.22	32.13	-0.02	1.80	7.91
parotids	20.69	18.78	21.97	21.36	24.34	32.13	1.28	2.58	7.79
pitutary	24.84	24.84	30.63	30.64	24.91	31.70	5.79	5.80	6.79
retinaLT	16.92	15.65	14.20	14.39	24.42	22.35	-2.72	-1.26	-2.07
retina Rt	18.38	17.37	14.24	14.49	24.35	22.68	-4.14	-2.88	-1.67
spinal cord	24.03	30.47	25.37	30.88	54.07	51.51	1.34	0.41	-2.56
TemporalLobeLt	24.00	25.41	31.26	31.49	55.03	56.01	7.26	6.08	0.98
temporallobeRT	24.08	25.40	30.58	30.69	52.77	53.86	6.50	5.29	1.10

Patient P3

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
brain	37.87	39.15	39.04	40.13	56.90	55.00	1.16	0.98	-1.90
brainSupra tent	38.00	39.58	39.85	40.66	56.90	55.00	1.85	1.08	-1.90
brain stem	39.95	44.06	38.26	43.28	55.43	54.89	-1.69	-0.78	-0.54
brainstemCore	40.74	44.40	38.69	43.61	55.41	54.97	-2.05	-0.79	-0.44
brain stemsurface	39.18	43.45	37.80	42.78	55.36	54.98	-1.38	-0.67	-0.37
cerebellum	37.94	38.51	36.64	37.28	55.92	54.85	-1.30	-1.23	-1.06
cochlea LT	37.98	37.99	35.94	35.95	38.40	36.24	-2.03	-2.04	-2.17
cochlea Rt	37.59	37.59	36.36	36.37	37.92	36.55	-1.23	-1.22	-1.37
cribriform	37.92	37.89	39.09	39.05	38.60	40.88	1.17	1.16	2.28
Hippo head Lt	41.32	41.50	44.41	44.45	46.88	50.43	3.08	2.95	3.55
hippohead Rt	38.67	38.66	43.45	43.16	39.56	47.05	4.78	4.50	7.49
hippo Lt	42.01	42.08	45.01	45.10	48.22	52.33	3.00	3.01	4.11
hippoRt	38.72	39.24	44.19	43.96	47.87	48.28	5.47	4.72	0.41
Hippo Tail Lt	44.32	44.38	47.74	47.78	48.22	52.11	3.42	3.41	3.90
hippo tai Rt	39.30	40.17	45.18	45.17	47.87	48.28	5.87	5.00	0.41
hypothalamus	47.14	47.21	50.03	50.04	55.06	54.52	2.89	2.83	-0.54
kidneyLt	0.00	2.07	7.43	8.81	36.15	33.14	7.43	6.74	-3.01
kidney rt	0.00	1.10	5.44	7.28	35.30	29.01	5.43	6.18	-6.29
lacrimal Lt	35.58	35.08	30.55	30.50	36.60	35.43	-5.03	-4.57	-1.17
lacrimal Rt	35.17	34.58	29.27	29.27	36.06	35.18	-5.89	-5.31	-0.88
lensLt	18.19	18.24	20.34	20.38	24.66	22.23	2.14	2.13	-2.43
lensRt	21.73	21.74	20.23	20.28	28.86	22.41	-1.50	-1.46	-6.45
lung Lt	0.00	4.09	6.12	7.90	38.97	37.76	6.11	3.81	-1.21
lung Rt	0.00	4.11	7.17	8.83	38.87	37.04	7.17	4.72	-1.84
lungs	0.00	4.11	6.57	8.40	38.97	37.76	6.57	4.30	-1.21
MastoidLt	36.26	36.29	35.87	35.31	37.93	37.17	-0.38	-0.98	-0.76
mastoidRt	36.08	36.11	35.25	34.68	37.80	37.34	-0.83	-1.43	-0.46
optichaism	38.41	38.40	41.83	41.88	38.57	43.24	3.42	3.48	4.67
optic nervLt	38.00	38.01	38.55	38.65	38.41	40.95	0.55	0.63	2.53
optic nerveRt	37.91	37.91	38.70	39.03	38.30	41.43	0.79	1.13	3.13
parotid_L_cagr	33.47	29.48	13.71	14.83	36.81	29.76	-19.76	-14.64	-7.05
parotid_R_cagr	31.55	28.91	13.70	15.17	36.94	32.38	-17.85	-13.74	-4.56
parotids	32.47	29.20	13.71	15.00	36.94	32.38	-18.77	-14.20	-4.56
pitutary	38.46	38.43	39.77	39.75	39.01	42.00	1.31	1.31	2.99
retinaLT	28.34	27.18	25.41	26.31	37.87	37.45	-2.94	-0.88	-0.42
retina Rt	28.88	26.73	25.42	26.14	37.40	36.95	-3.46	-0.58	-0.45
scalp	34.51	33.68	32.19	31.00	39.49	40.92	-2.32	-2.68	1.43
spinal cord	36.34	36.38	36.10	36.09	38.31	37.72	-0.24	-0.29	-0.58
TemporalLobeLt	39.50	39.78	41.36	41.52	54.80	54.65	1.86	1.74	-0.14
temporallobeRT	39.96	37.35	40.21	40.33	54.19	54.08	0.25	2.98	-0.11
thecalsac	36.51	36.49	36.21	36.15	37.26	37.72	-0.30	-0.34	0.46

Patient P4

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bladder	0.00	2.21	6.59	8.66	53.69	49.23	6.59	6.46	-4.45
bowel large	0.01	4.59	11.64	14.25	56.38	56.36	11.64	9.66	-0.03
bowel small	0.00	0.15	1.27	5.81	55.77	54.34	1.27	5.66	-1.43
fermur left	0.00	0.00	0.99	1.54	0.01	4.89	0.99	1.54	4.89
fermur right	1.07	11.64	3.67	7.63	55.78	55.91	2.60	-4.01	0.13
growth plate	0.01	1.42	2.44	2.50	23.50	6.02	2.44	1.08	-17.48
Growth plate left	0.00	0.00	1.10	1.26	0.01	3.18	1.10	1.26	3.17
growth plate right	0.99	2.81	3.68	3.72	23.46	6.02	2.69	0.91	-17.43
kidneyLt	0.00	0.00	0.01	0.09	0.01	0.64	0.00	0.09	0.64
kidney rt	0.00	0.00	0.01	0.25	0.01	1.54	0.01	0.25	1.53
non target body	0.00	3.47	0.77	5.82	58.05	57.26	0.77	2.35	-0.79
non target bowel	0.00	2.34	5.44	10.07	56.23	55.96	5.44	7.73	-0.27
rectum	0.01	0.69	7.21	7.18	12.74	19.40	7.20	6.49	6.66

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OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
brain	25.00	29.73	24.25	29.14	56.74	55.60	-0.75	-0.59	-1.14
brainSupra tent	24.75	27.06	24.16	26.27	56.33	54.99	-0.60	-0.79	-1.34
brain stem	51.51	47.96	52.30	49.68	56.38	55.48	0.79	1.72	-0.90
brainstemCore	50.00	48.04	50.53	49.55	55.97	55.48	0.54	1.51	-0.49
brain stemsurface	53.12	47.95	53.97	49.86	56.39	55.46	0.85	1.91	-0.92
cerebellum	51.88	47.44	48.35	47.39	56.74	55.49	-3.53	-0.05	-1.26
cochlea LT	25.38	25.40	34.27	34.27	26.13	34.79	8.89	8.88	8.67
cochlea Rt	30.85	30.89	38.66	38.70	33.23	39.61	7.82	7.81	6.38
cribriform	24.77	24.78	24.35	24.59	25.15	27.64	-0.42	-0.19	2.49
heart	0.00	0.20	7.65	8.41	21.87	22.58	7.65	8.21	0.71
Hippo head Lt	26.30	27.49	32.10	32.32	39.18	37.84	5.80	4.83	-1.33
hippohead Rt	26.63	27.30	36.28	36.35	34.01	41.05	9.65	9.05	7.04
hippo Lt	29.76	33.41	32.81	33.59	52.40	45.30	3.05	0.18	-7.10
hippoRt	28.59	30.91	36.35	36.35	47.26	41.05	7.77	5.44	-6.21
Hippo Tail Lt	44.67	43.62	35.07	35.60	52.40	45.30	-9.60	-8.01	-7.10
hippo tai Rt	38.54	38.15	36.48	36.30	47.26	39.48	-2.07	-1.85	-7.78
hypothalamus	32.22	33.62	30.61	32.80	51.60	53.60	-1.61	-0.82	2.00
kidneyLt	0.04	2.90	6.03	7.48	23.65	23.42	5.99	4.59	-0.23
kidney rt	0.25	4.54	7.69	8.96	4.54	23.21	7.44	4.42	18.66
lacrimal Rt	23.24	22.57	17.96	18.22	23.78	22.95	-5.27	-4.35	-0.82
lensLt	16.20	16.03	14.45	14.45	18.55	15.13	-1.75	-1.59	-3.42
lensRt	12.67	12.81	13.69	13.81	19.47	15.12	1.02	1.01	-4.35
lung Lt	0.00	1.06	2.59	3.55	23.69	23.41	2.59	2.49	-0.28
lung Rt	0.00	3.09	5.22	6.28	24.03	24.08	5.22	3.19	0.05
lungs	0.00	2.30	3.68	5.21	24.03	24.08	3.68	2.91	0.05
MastoidLt	30.15	28.83	31.69	31.50	32.28	36.72	1.54	2.67	4.44
mastoidRt	30.27	29.16	33.97	33.84	33.35	40.51	3.69	4.68	7.16
non target body	0.00	3.43	3.13	6.36	54.80	53.42	3.12	2.94	-1.38
optichaism	25.08	25.08	29.74	29.73	25.12	30.53	4.66	4.65	5.41
optic nervLt	24.86	24.84	26.76	26.13	25.10	29.35	1.90	1.29	4.25
optic nerveRt	24.93	24.89	27.03	26.73	25.13	30.35	2.11	1.84	5.22
parotid_L_cagr	19.49	18.46	21.47	21.53	27.61	30.29	1.98	3.07	2.68
parotid_R_cagr	19.63	18.03	22.79	22.82	26.86	32.98	3.16	4.79	6.12
parotids	19.56	18.25	22.04	22.17	27.61	32.98	2.49	3.92	5.37
pitutary	25.08	25.07	32.81	32.78	25.25	33.75	7.74	7.71	8.50
retinaLT	21.35	20.38	17.96	18.22	24.72	24.05	-3.39	-2.16	-0.67
retina Rt	18.52	17.31	16.61	16.83	24.65	22.94	-1.91	-0.48	-1.71
scalp	22.36	22.56	20.42	20.48	31.01	33.20	-1.94	-2.09	2.19
spinal cord	23.29	23.86	23.83	24.34	47.58	48.52	0.54	0.48	0.94
TemporalLobeLt	24.71	27.57	27.67	28.70	56.11	53.28	2.97	1.13	-2.83
temporallobeRT	24.50	27.16	29.35	29.72	56.13	54.38	4.85	2.56	-1.75
thecalsac	23.66	23.65	24.24	24.24	23.73	24.49	0.58	0.59	0.76
zbones	23.35	23.37	23.82	23.92	51.47	50.97	0.47	0.55	-0.50

Patient P5

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OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
brain	24.77	28.10	24.18	27.44	56.44	57.88	-0.59	-0.67	1.43
brainSupra tent	24.61	25.96	24.12	25.23	53.88	53.76	-0.49	-0.73	-0.13
brain stem	46.78	44.10	43.99	42.59	56.15	56.40	-2.79	-1.51	0.26
brainstemCore	46.82	44.66	43.67	42.21	55.67	56.28	-3.15	-2.45	0.61
brain stemsurface	47.44	43.98	44.77	43.35	56.16	56.40	-2.67	-0.63	0.25
cerebellum	42.70	43.14	39.77	42.35	56.44	57.57	-2.93	-0.80	1.13
cochlea LT	24.68	24.69	34.61	34.59	25.23	35.37	9.92	9.90	10.14
cochlea Rt	25.68	25.74	36.53	36.58	27.24	37.91	10.86	10.83	10.67
cribriform	24.64	24.64	24.21	24.15	25.24	24.49	-0.44	-0.49	-0.75
Esophagus	9.05	10.28	20.97	20.51	23.63	23.73	11.92	10.22	0.10
heart	0.00	0.63	7.89	8.56	24.13	21.73	7.89	7.93	-2.41
Hippo head Lt	26.06	26.53	27.91	28.24	31.10	32.58	1.85	1.71	1.48
hippohead Rt	27.80	28.21	26.73	27.43	33.76	33.89	-1.07	-0.78	0.13
hippo Lt	32.82	31.65	26.51	27.10	40.60	32.58	-6.31	-4.55	-8.02
hippoRt	32.42	31.59	26.12	26.85	39.94	33.89	-6.30	-4.74	-6.05
Hippo Tail Lt	34.50	34.20	25.98	26.52	40.60	32.47	-8.52	-7.69	-8.13
hippo tai Rt	34.77	34.88	25.87	26.26	39.94	33.29	-8.90	-8.62	-6.66
hypothalamus	25.81	27.17	24.57	24.62	33.25	25.28	-1.24	-2.55	-7.98
kidneyLt	0.00	2.61	6.91	8.09	23.58	23.17	6.91	5.48	-0.41
kidney rt	0.10	4.30	9.09	9.99	23.52	23.76	8.99	5.70	0.24
lacrimal Rt	23.00	22.39	16.63	16.89	23.66	21.11	-6.37	-5.50	-2.55
lensLt	14.39	14.54	13.27	13.31	19.55	21.67	-1.12	-1.23	2.12
lensRt	17.00	16.79	13.37	13.37	19.86	14.28	-3.63	-3.42	-5.59
lung Lt	0.00	2.44	7.00	8.34	24.78	14.19	6.99	5.90	-10.59
lung Rt	0.00	4.59	7.61	8.75	25.68	23.16	7.61	4.16	-2.51
lungs	0.00	3.63	7.31	8.57	25.68	24.15	7.31	4.94	-1.53
MastoidLt	23.50	23.51	31.69	31.27	26.68	37.25	8.19	7.76	10.57
mastoidRt	23.76	24.46	32.64	32.20	32.12	39.19	8.88	7.75	7.06
non target body	0.00	3.94	5.35	7.76	52.86	48.81	5.35	3.81	-4.06
optichaism	24.91	24.91	24.67	24.66	24.97	24.78	-0.25	-0.25	-0.19
optic nervLt	24.70	24.65	24.56	23.69	24.93	24.75	-0.14	-0.95	-0.18
optic nerveRt	24.70	24.69	24.24	23.83	24.90	26.65	-0.46	-0.86	1.74
parotid_L_cagr	22.23	19.78	18.69	18.30	24.13	26.57	-3.54	-1.48	2.44
parotid_R_cagr	22.96	21.48	20.24	19.63	24.29	28.34	-2.72	-1.86	4.06
parotids	22.67	20.59	19.22	18.93	24.29	28.34	-3.46	-1.66	4.06
pitutary	24.85	24.86	25.80	26.32	24.97	30.10	0.94	1.46	5.13
retinaLT	19.19	18.34	15.64	16.01	24.44	21.66	-3.54	-2.33	-2.77
retina Rt	21.69	20.43	15.35	16.03	24.53	22.33	-6.34	-4.40	-2.19
scalp	22.58	22.97	21.27	21.40	30.65	30.77	-1.31	-1.58	0.13
spinal cord	23.43	23.72	23.97	24.02	40.28	32.37	0.54	0.30	-7.92
TemporalLobeLt	24.25	26.01	25.14	27.33	53.41	51.48	0.88	1.32	-1.94
temporallobeRT	24.25	25.79	24.79	26.73	52.67	50.28	0.54	0.94	-2.39
thecalsac	23.78	23.79	23.83	23.89	23.96	24.70	0.05	0.10	0.75
zbones	23.43	23.20	23.88	23.82	40.35	34.36	0.45	0.62	-5.99

Patient P6

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Patient P7

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bladder	0.00	0.02	0.51	0.58	3.54	2.15	0.50	0.56	-1.38
bones	21.41	20.06	21.13	17.44	23.28	22.78	-0.28	-2.61	-0.50
bowel	1.58	7.12	12.60	13.10	21.87	22.05	11.02	5.98	0.18
bowel large	0.00	2.58	8.26	8.77	21.99	21.73	8.25	6.18	-0.26
bowel small	0.24	5.62	10.50	11.28	22.34	22.10	10.27	5.66	-0.24
growthplate left	0.00	0.00	0.26	0.26	0.00	0.27	0.26	0.26	0.27
growthplateright	0.00	0.00	0.23	0.23	0.00	0.25	0.23	0.23	0.24
growthplates	0.00	0.00	0.25	0.25	0.00	0.27	0.25	0.24	0.27
kidneyLt	0.07	3.63	1.04	4.27	22.05	21.50	0.97	0.64	-0.55
kidney rt	6.15	8.71	6.11	8.65	22.01	21.58	-0.04	-0.06	-0.44
kidneys	1.25	6.03	3.39	6.33	22.05	21.58	2.14	0.31	-0.47
liver	0.00	0.04	3.58	3.65	3.78	9.41	3.58	3.61	5.63
non target body	0.00	1.40	0.18	2.15	23.39	22.40	0.17	0.76	-0.99
non target bowel	0.23	5.58	10.48	11.25	22.34	22.09	10.25	5.68	-0.25
rectum	0.06	1.12	0.33	0.39	10.93	0.90	0.28	-0.73	-10.03
skin	0.01	1.30	0.20	2.15	23.16	21.80	0.19	0.85	-1.36
spinal cord	0.00	0.01	0.30	0.35	1.32	0.77	0.30	0.34	-0.55
vertebral bodies	21.37	21.40	21.43	21.45	22.09	22.33	0.06	0.05	0.24

Patient P8

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bones	50.33	47.48	51.07	48.57	52.10	54.31	0.74	1.08	2.21
breast	0.00	0.00	2.23	3.70	0.00	13.42	2.22	3.70	13.42
Esophagus	37.91	31.62	43.47	36.58	50.94	53.55	5.56	4.95	2.60
heart	0.00	0.40	1.29	3.50	33.23	40.56	1.29	3.10	7.33
lung Lt	0.01	6.53	11.32	11.96	52.20	52.85	11.31	5.43	0.64
lung Rt	0.11	10.19	9.23	13.95	53.66	52.50	9.12	3.76	-1.16
lungs	0.04	8.58	10.14	13.07	53.66	52.85	10.10	4.50	-0.82
non target body	0.00	2.29	0.28	4.69	53.66	54.26	0.28	2.40	0.59
non target lung	0.04	8.56	10.13	13.06	53.66	52.85	10.09	4.50	-0.82
spainal cord	49.49	36.74	49.52	35.29	50.99	51.08	0.03	-1.45	0.10
thyroid	1.20	2.29	24.57	24.19	13.66	38.85	23.37	21.90	25.19
zspinal vord +3mn	49.85	36.91	49.71	35.76	51.56	52.34	-0.13	-1.15	0.78

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OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
brain	37.69	39.48	36.82	38.82	56.41	55.41	-0.87	-0.66	-1.00
brainSupra tent	37.53	38.31	36.58	37.32	55.29	54.89	-0.94	-0.99	-0.40
brain stem	50.22	48.40	52.48	51.16	54.90	55.33	2.27	2.76	0.43
brainstemCore	50.30	48.81	52.61	51.57	53.82	55.33	2.31	2.76	1.52
brain stemsurface	50.20	47.96	52.30	50.73	54.90	55.27	2.10	2.77	0.37
cerebellum	47.08	47.52	47.73	48.28	56.41	55.40	0.64	0.75	-1.01
cochlea LT	37.83	37.87	39.46	39.54	38.47	41.13	1.63	1.67	2.65
cochlea Rt	37.99	37.98	40.15	40.13	38.55	40.56	2.16	2.15	2.01
cribriform	37.08	37.08	35.90	35.94	37.76	38.93	-1.18	-1.14	1.17
Esophagus	0.00	0.49	17.99	18.44	21.55	31.26	17.99	17.95	9.71
heart	0.00	0.03	7.14	7.42	12.75	15.00	7.14	7.39	2.25
Hippo head Lt	38.49	39.04	41.71	41.80	43.85	44.84	3.22	2.76	1.00
hippohead Rt	38.34	38.73	40.86	40.91	41.67	42.34	2.52	2.19	0.67
hippo Lt	43.99	43.32	41.98	41.86	50.97	47.84	-2.02	-1.46	-3.13
hippoRt	41.73	41.19	40.84	40.51	46.58	42.66	-0.89	-0.68	-3.92
Hippo Tail Lt	46.66	46.48	42.37	41.90	50.97	47.84	-4.29	-4.58	-3.13
hippo tai Rt	42.81	42.98	40.80	40.20	46.58	42.66	-2.01	-2.78	-3.92
hypothalamus	37.94	38.99	37.49	37.71	46.40	42.51	-0.44	-1.28	-3.89
kidneyLt	0.00	0.46	9.18	10.13	31.30	29.89	9.17	9.66	-1.40
kidney rt	0.00	0.74	8.14	9.30	35.06	31.04	8.13	8.56	-4.02
lacrimal Lt	35.19	30.51	24.93	24.73	37.06	30.36	-10.26	-5.79	-6.70
lacrimal Rt	35.72	32.16	23.90	24.11	37.03	29.78	-11.82	-8.05	-7.24
lensLt	23.39	23.13	21.56	21.57	28.26	23.22	-1.83	-1.56	-5.04
lensRt	21.53	20.99	20.64	20.17	27.95	21.83	-0.89	-0.83	-6.12
lung Lt	0.00	1.59	7.21	8.75	39.58	37.43	7.20	7.17	-2.16
lung Rt	0.00	2.18	8.31	9.90	40.84	36.89	8.30	7.73	-3.95
Lungs	0.03	1.89	7.77	9.35	40.84	37.43	7.74	7.46	-3.41
MastoidLt	38.08	38.27	37.92	37.54	41.22	45.01	-0.17	-0.73	3.78
mastoidRt	37.10	37.17	34.48	33.95	40.89	42.72	-2.62	-3.22	1.83
non target body	0.00	4.27	4.83	7.84	56.22	55.35	4.83	3.57	-0.87
non target brain	37.66	39.11	36.77	38.46	56.22	55.35	-0.89	-0.65	-0.86
optichaism	37.74	37.74	40.88	40.86	37.86	41.94	3.14	3.12	4.08
optic nervLt	37.21	37.19	35.09	35.03	38.22	40.91	-2.11	-2.16	2.69
optic nerveRt	37.40	37.39	35.00	34.76	38.73	40.82	-2.40	-2.64	2.10
parotid_L_cagr	27.66	26.86	15.89	16.29	38.24	26.88	-11.77	-10.57	-11.36
parotid_R_cagr	31.51	28.32	16.42	16.50	37.67	28.53	-15.09	-11.82	-9.13
parotids	29.62	27.56	16.09	16.39	38.24	28.53	-13.54	-11.17	-9.70
pituitary	37.90	37.89	40.42	40.43	38.30	41.59	2.51	2.54	3.29
retinaLT	28.70	27.12	23.73	23.73	37.32	29.88	-4.98	-3.39	-7.44
retina Rt	29.27	28.05	23.06	23.31	37.48	31.35	-6.21	-4.74	-6.13
scalp	34.25	33.38	16.84	16.45	39.50	28.64	-17.41	-16.93	-10.86
spinal cord	39.56	38.66	39.60	38.64	49.41	52.52	0.04	-0.02	3.11
TemporalLobeLt	38.03	38.88	38.83	39.24	54.58	54.47	0.80	0.36	-0.10
temporallobeRT	38.01	38.63	39.22	39.03	50.81	48.92	1.22	0.40	-1.88
thecalsac	36.48	36.53	36.45	36.44	37.46	37.31	-0.03	-0.09	-0.15
vertebral bodies	25.64	20.98	30.66	29.99	42.68	41.15	5.03	9.01	-1.52

Patient P9

Patient P10

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
brain	23.60	30.78	24.95	32.64	56.92	55.84	1.35	1.85	-1.08
brainSupra tent	23.51	26.87	24.54	29.03	55.61	55.66	1.03	2.16	0.05
brain stem	53.42	53.23	53.22	52.92	54.40	54.32	-0.20	-0.31	-0.08
chiasma	34.70	35.07	37.65	38.48	50.65	50.62	2.95	3.41	-0.03
cochlea LT	28.47	28.64	42.02	42.17	33.63	47.30	13.55	13.53	13.67
cochlea Rt	29.24	29.56	42.66	42.85	35.63	46.98	13.43	13.30	11.35
cord	23.42	23.87	23.57	24.03	50.73	52.20	0.15	0.16	1.47
eye left	2.20	3.97	10.13	13.12	18.92	26.07	7.93	9.15	7.15
eye right	1.33	2.99	19.22	16.78	17.42	26.41	17.88	13.79	8.99
heart	0.00	0.23	7.72	8.08	8.07	19.35	7.72	7.85	11.28
hippo Lt	48.55	47.51	50.16	49.13	55.33	54.70	1.62	1.62	-0.63
hippoRt	49.78	48.50	50.06	49.92	55.33	54.86	0.28	1.42	-0.47
hypothalamus	39.45	39.75	31.90	33.12	51.30	49.18	-7.55	-6.63	-2.12
inner ear left	31.34	32.48	43.05	43.38	47.33	53.40	11.72	10.90	6.07
inner ear right	31.94	32.84	43.16	43.73	46.66	54.45	11.21	10.89	7.79
kidneyLt	0.00	0.37	1.95	3.12	17.48	21.41	1.94	2.75	3.93
kidney rt	0.00	0.48	2.21	3.89	18.87	22.56	2.21	3.41	3.69
lensLt	0.94	1.01	4.73	4.89	2.13	8.16	3.78	3.88	6.03
lensRt	0.67	0.75	5.84	5.97	1.93	10.81	5.18	5.22	8.87
lung Lt	0.00	1.21	2.44	3.87	21.80	22.62	2.43	2.66	0.82
lung Rt	0.01	1.48	4.03	5.58	23.14	23.40	4.02	4.09	0.25
Lungs	0.00	1.21	3.17	4.82	21.78	23.40	3.16	3.61	1.62
optichaism	28.15	28.35	33.33	33.43	32.15	37.88	5.17	5.08	5.73
optic nervLt	21.89	18.79	26.42	25.11	27.38	34.91	4.53	6.32	7.52
optic nerveRt	22.14	18.10	27.13	27.59	26.64	37.35	4.99	9.48	10.71
parotid_L_cagr	1.88	3.06	22.69	23.03	19.50	42.08	20.81	19.97	22.59
parotid_R_cagr	2.43	4.08	24.20	23.44	20.13	40.67	21.77	19.36	20.54
parotids	2.13	3.55	23.67	23.23	20.13	42.08	21.55	19.68	21.95
pitutary	32.96	33.26	39.36	39.61	41.68	45.74	6.40	6.35	4.07
skin	0.00	2.72	0.89	5.41	56.92	55.91	0.88	2.69	-1.02
spinalkanal	23.43	24.65	23.56	24.70	54.75	54.70	0.13	0.05	-0.05
TMJ left	20.01	19.66	36.85	35.95	24.38	38.42	16.85	16.29	14.04
TMJ right	20.48	20.05	40.87	41.03	26.36	44.75	20.40	20.98	18.39
Testicles	0.00	0.00	0.03	0.56	0.00	0.16	0.03	0.56	0.15
Thyroid	0.00	0.00	17.20	17.50	0.76	22.52	17.19	17.50	21.76
TemporalLobeLt	23.93	28.39	37.69	37.03	55.40	55.15	13.76	8.65	-0.25
temporallobeRT	24.15	28.99	37.32	36.18	54.98	55.45	13.17	7.19	0.46

Patient P11

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
bowel large	0.00	0.45	0.65	3.79	22.80	23.48	0.64	3.34	0.68
bowel small	0.03	4.10	1.12	6.42	23.10	23.49	1.09	2.32	0.39
heart	0.00	0.28	1.07	4.87	17.70	23.34	1.06	4.59	5.64
kidneyLt	8.74	9.79	1.24	2.38	22.95	21.42	-7.50	-7.41	-1.53
kidneyRt	19.67	16.75	23.18	22.78	23.38	23.77	3.51	6.03	0.39
liver	2.94	6.06	3.87	10.60	24.11	23.63	0.93	4.54	-0.48
lung Lt	0.00	0.20	0.35	0.47	20.31	15.72	0.35	0.27	-4.59
lung Rt	0.00	2.13	0.65	2.11	24.37	23.46	0.65	-0.02	-0.91
lungs	0.00	1.36	0.51	1.46	24.37	23.46	0.50	0.10	-0.91
non target body	0.00	2.22	0.51	3.58	23.96	24.08	0.51	1.37	0.12
non target bowel	0.00	1.51	0.79	4.45	22.91	23.49	0.79	2.93	0.57
non target lung	0.00	1.14	0.50	1.24	24.10	23.46	0.50	0.11	-0.65
spinal cord	0.00	1.14	17.88	11.81	22.55	22.59	17.88	10.68	0.04
stomach	0.01	3.26	1.92	6.72	23.15	22.76	1.92	3.46	-0.38
vertebrace	20.21	19.64	22.13	18.80	23.39	23.77	1.92	-0.83	0.38

OAR	Prmed	Prmea	Phmed	Phmea	Prmax	Phmax	Phmed-Prmed	Phmea-phmea	Phmax-Prmax
						Patient P12			
Esophagus	19.01	15.79	18.18	15.47	22.32	21.25	-0.83	-0.32	-1.08
heart	0.00	0.75	8.82	9.19	21.36	21.08	8.82	8.44	-0.28
liver	0.00	0.00	0.18	0.24	0.46	3.22	0.18	0.24	2.76
lung Lt	2.49	8.32	13.24	12.25	23.03	21.96	10.75	3.93	-1.07
lung Rt	0.00	1.16	4.24	3.94	20.85	20.06	4.24	2.78	-0.79
lungs	0.00	3.99	4.81	7.23	23.03	21.96	4.80	3.23	-1.07
non target body	0.00	1.45	0.26	2.57	22.84	22.06	0.26	1.13	-0.77
non target lung	0.00	3.94	4.80	7.18	23.03	21.96	4.79	3.24	-1.07
skin	0.00	0.98	0.21	1.87	22.09	21.11	0.21	0.89	-0.99
spinal cord	10.69	10.73	3.17	10.11	22.03	21.89	-7.52	-0.63	-0.13
stomach	0.00	0.00	0.46	0.50	0.56	1.17	0.46	0.49	0.61