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The Development of Modern Radiation Therapy

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Abstract

Purpose of Review Radiation therapy is a treatment modality used in the management of patients with cancer that utilizes ionizing radiation to kill cells. Herein, we provide a brief review of basic radiobiology principles to describe the mechanisms of radiation effects and injuries.

Recent Findings With technologic advances, radiation therapy has evolved significantly over the past several decades. Such advances have changed the way in which radiation reaches target tissue while sparing normal tissue, and subsequently the doses of radiation that can be administered.

Summary From a rehabilitation standpoint, it is critical to understand the type of radiation therapy used, the dose prescribed, and the volume to which the radiation therapy was administered when treating a patient with a radiation-related injury. We describe the fundamentals of radiation therapy planning and administration as well as commonly utilized modern radiation therapy techniques.

Keywords Radiotherapy · Intensity-modulated Radiation Therapy · Stereotactic Body Radiation Therapy · Stereotactic Radiosurgery · Proton Bean Radiation Therapy · Radiation Injury

Introduction

Pierre Currie first noted that radiation was biologically active when he developed a burn on his chest where he frequently kept a test tube of radioactive radium in the pocket of his shirt [1]. Steady technologic advances in the development of linear accelerators, medical imaging, and computing have all contributed to the field of modern radiation therapy, a powerful non-invasive treatment modality that is able to provide curative treatment of even the most deep seated tumors that may lay beyond a surgeon's knife [2]. This is accomplished by utilizing high precision photon and charged particle beams that tightly conform to the three-dimensional tumor target, while minimizing radiation dose to the surrounding normal tissue, using near real-time three-dimensional imaging to verify that treatment is being accurately placed [3, 4]. In the case of tumor targets in mobile organs such as many parts of the lung and abdomen, tumors can be accurately tracked during respiration to provide highly conformal therapy during respiration [5]. Built in computerized tomography (CT) and magnetic resonance (MR) imaging can be utilized to verify target and normal organ positioning during treatment to allow accurate placement of treatment beams within a millimeter of uncertainty [3]. The combination of conformal radiation and advanced imaging has allowed radiation oncologist to treat tumors safely and effectively.

What is Radiation?

Dose and Fractionation

The basic concepts upon which radiation therapy treatment regimens are constructed are the dose of radiation, expressed as units of Gray (Gy), and the number of fractions or treatments administered [2]. One Gray is an expression of energy per unit mass and is defined as 1 J/kg. In terms of the dose of radiation, the dose per fraction and the total dose of radiation are important considerations. The type of tissue receiving

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radiation can also factor into how radiation effects the target tissue in question. Generally, a higher dose of radiation results in a greater biologic impact. This is true for both dose of radiation per fraction and the total dose of radiation. This relationship is often expressed as the relative biologic effective dose or BED [2]. The BED calculation is dependent upon the dose per fraction (*D*), the number of fractions (*N*), and the relative radiation sensitivity of the tissue or tumor in question (α/β) [2]. In this model, a lower α/β represents relatively low radioresponsiveness, while a higher α/β suggests a more radioresponsive tissue.

The more mitotically active a cell is, the more radioresponsive it tends to be [6]. Normal tissues tend to be less radioresponsive than many cancers, but some malignancies, such as many sarcomas, melanomas, and renal cell carcinomas, are thought to have low α/β values and are therefore less sensitive to radiation [2]. Examples of radiosensitive tissue histologies include almost all liquid tumors such as lymphomas and leukemias and breast cancer as an example of a solid malignancy.

Hematopoietic bone marrow, gut mucosal epithelium, and the skin are examples of tissues with a high α/β value and are considered radiosensitive tissues, while muscle, bone, and nervous tissue in adults are thought of as low α/β tissue [7]. Although highly mitotically active normal tissues respond to radiation quickly, they are also often able to recover from radiation injury [6]. Hence, radiation effects on radiosensitive tissues like the skin or oral mucosa are less detrimental as these tissues are able to heal from the effects of radiation by repopulating cells that are lost. Tissues that are less radiation sensitive and less mitotically active may be unable to replace cells lost to radiation damage, and these tissues tend to exhibit permanent injury [2]. These types of injury typically manifest months to years after radiation treatment and are often labeled as late effects of radiation. Late complications of radiation may never heal and are thus more serious complications of treatment. Early effects of radiation are often transient and quite common, while late effects are fortunately rare when radiation is given with careful thought.

The dose of radiation given to a tumor must be tempered against the likelihood of radiation-related toxicity to the surrounding normal tissues. The volume of an organ exposed to radiation also increases the risk of a radiation complication [8]. As a result, radiation oncologists strive to maximize the radiation dose to the tumor while minimizing the exposure of normal tissue. In addition to radiation dose and volume factors, systemic therapies such as chemotherapy can also increase the risk of radiation-related toxicity as they may make cells more susceptible to damage from radiation. The higher risk of radiation complications with anthracycline-based chemotherapy and gemcitabine-based systemic treatment are well documented [6, 9, 10].

There are several mechanisms that are thought to be responsible for late effects of radiation therapy. One is due to the loss of cells in the organ in question [5, 8]. Radiation may result in the death of normal cells as part of treatment. Lost cells in tissues that respond late to radiation are often not replaced. For example, if cells are lost from the psoas muscle secondary to radiation, psoas weakness can result from the physical loss of effector cells. Radiotherapy may also cause microvascular damage over time. Endothelial cells in the microvascular can thicken over time as a result of radiation exposure [6, 11, 12]. If the endothelial lining becomes too thickened, it may result in luminal narrowing that reduces and/or prevents the transit of red blood cells to tissues. This can result in downstream hypoxia and subsequent necrosis. Ischemic injuries can also result in an over-inflammatory response, which can lead to excessive fibrosis within previously irradiated tissues [6]. On occasion, the fibrosis results in nerve and vascular entrapment, resulting in neuropathy and ischemia, further complicating the function of normal tissues downstream of the injury [13, 14]. In the example of psoas injury, weakness can be further exasperated by chronic ischemia and denervation effects which further cause weakness.

Physiatrists may better understand how to help patients who suffer from late effects of radiation by better understanding the region and volume to which the radiation was given, the dose of radiation per fraction, and the total dose prescribed.

When radiation is given to a small volume of tissue with a treatment regimen with a lower BED (a lower dose per fraction, and a lower total dose), radiation toxicity is less likely [2]. When a treatment with a high BED is required to successfully treat a malignancy, extra care must be taken to minimize the volume and dose of radiation that is inadvertently delivered to surrounding normal tissues [15]. An example of this is using stereotactic radiosurgery, or precise high-dose radiation, to treat a melanoma brain metastasis. Melanomas tend to be resistant to radiation and require high BED dosing [16]. Giving an entire course of treatment in a single session is an effective way to overcome the inherent radioresistance of melanoma [17, 18]. The brain, however, is a critical organ and does not easily tolerate the high BED needed to kill melanoma brain metastases [2]. Stereotactic radiosurgery is a treatment technique that provides high-dose radiation within the metastasis, but, at the outside edge of the tumor, provides a very steep reduction of radiation dose to the surrounding brain tissue [19–21]. This is achieved by using multiple beams of radiation from many different angles, with each beam conforming to the shape that the tumor presents from each angle, with each beam passing through the center of the tumor. This allows the radiation to be highly concentrated inside the tumor, while significantly

less radiation is delivered to the normal surrounding brain parenchyma.

To precisely target the tumor, the patient's skull is immobilized during treatment using a custom thermoplastic mask that effectively minimizes movement during the delivery of radiation [8]. Cone beam CT imaging is also used during treatment to verify that the radiation beams are aimed precisely at the target, with accuracy within 1 mm [15]. With this technique, a high BED is given within the tumor, while the brain dose rapidly decreases from 100% at the tumor edge to less than 50%, 5 mm away. Typically, radiosurgery is able to treat brain metastasis less than 2 cm in diameter with a better than 90% probability of tumor control 1-year post-treatment, while the risk of radiation brain necrosis is less than 10% [22•].

An extreme opposite example is total body irradiation. Total body irradiation (TBI) may be done in preparation for a bone marrow transplant, where the goal of treatment is to eradicate the body's entire bone marrow reserve [6, 8]. The radiation field or volume that receives radiation encompasses the whole body. In this case, the dose of radiation that the whole body can tolerate is less than one third of the dose that can be safely given to a brain metastasis using stereotactic radiosurgery.

Radiation Therapy Treatment Workflow

Radiation therapy is a multi-step process. The first step in preparing a patient for radiation therapy is called simulation. At the time of simulation, all the necessary preparation for radiation therapy is undertaken. The patient is often placed in a custom immobilization device. These devices are designed to position the patient in a reproducible position for treatment and are often created during simulation [8, 15]. In the case of simulation for the treatment of a lumbar spine metastasis, a body mold is custom created for the patient. This is a noninvasive device which is made to exactly fit the patient's body contour, with the spine as straight as comfortably possible. The patient will lay in the device for each session of radiation. The mold will help ensure that the patient presents in the same geometric position that reproduces the position of the spine and the metastasis at the time of simulation for each radiation treatment. The 3D position of the patient and the tumor at the time of simulation is what the radiation treatment is based upon and needs to be accurately reproduced for each treatment. Another important function of the mold is to prevent inadvertent patient motion during the delivery of radiation. The effective use of immobilization devices allows for smaller margins of high-dose radiation around the tumor, since there can be a higher degree of confidence that the tumor is geometrically where it should be (where it was at the time of simulation an treatment planning) for treatment [8]. When the degree of uncertainty regarding the position of the tumor is high, then a larger margin of normal tissue needs to be included to ensure that the tumor receives the intended dose of radiation. However, because this increases the dose of radiation that is delivered to normal tissue and subsequently the risk of complications, lower BED treatment schedules are often prescribed to keep the risk of complications at a reasonably low level. When low BED treatment schedules are used, as in the case palliative radiation for breast cancer bone metastases, then immobilization is often not necessary, because a wider margin of normal tissue can be utilized without significantly increasing the risk of normal tissue complications.

Another important step in simulation is to acquire a 3D high-resolution CT scan of the section of the body to be treated. This scan, with the patient properly positioned, is the basis of dose calculations for treatment. The CT scan is reconstructed to create a virtual model of the patient's anatomy including the tumor to be treated and nearby normal structures. The structures are outlined virtually to create a contour map [3]. In this virtual environment, the number of radiation beams, the appropriate beam angles for each beam, and the size and shape of each beam can be optimized given the shape and size of the tumor to be treated, while taking into account the intended dose, as well as the radiation dose tolerance of normal tissues nearby [23].

Organ motion can also be accounted for during this process of treatment planning [8]. For example, when planning radiation treatment for an L1 vertebral body metastasis, the location of the tumor, the amount of the vertebral body and other involved bony spine elements, and the intended target volume must be accurately identified in the treatment planning software [24, 25]. Radiosensitive organs such as the spinal cord, the early roots of the cauda equina, and nearby bowel, stomach, liver, and kidneys must also be correctly identified [3]. Each of these organs have unique tolerances to radiation based on the volume of the organ that will be exposed to radiation. Modern computer algorithms can optimize how the prescribed radiation dose is best delivered to the target while keeping the dose to the nearby organs at risk at acceptable levels. The result of this meticulous process is the treatment plan.

To better understand the mechanism and potential effects of radiation, it is important to be able to comprehend a review of the dose distribution. The dose distribution is a map of how much radiation is given to a specific part of the patient's body based on the treatment plan [8]. Similar to a contour map, levels of dose intensity are overlayed on an image of the patient, usually a CT scan. By reviewing the dose distribution, the physiatrist can visually assess the site of prior treatment and understand the dose of radiation that might have been given to the bowel or kidney, in the case of a high lumbar spine metastasis. Typically, only tissue structures within the high-dose region need be considered.

For example, in the case of a spine metastasis treated with stereotactic body radiation therapy at L3, the tissues of concern would include spinal cord, cauda equina, paraspinal muscles, L3 nerve roots, and bone. Tissues outside the high-dose region such as the kidney, bowel, or stomach are not likely to undergo late radiation effects that might result in functional impairment (see Fig. 1).

When radiation is delivered to the patient, the patient is first placed in the mold created at the time of simulation and images of the target area are taken [8]. By comparing the reference simulation images with those obtained at the time of treatment, off sets in the X, Y and Z planes, as well as rotational corrections in pitch, yaw, and role, can be calculated to shift the patient into the reference position. Once imaging has verified that the correct position has been achieved, the treatment plan can be executed to deliver the radiation treatment as intended.

Modern Radiation Treatment Techniques

Intensity-Modulated Radiation Therapy

One of the most impactful advances in radiation therapy is intensity-modulated radiotherapy or IMRT [3, 4]. IMRT can create clouds of radiation in a patient that is sculpted to match the 3D characteristic of the target volume. This is accomplished by matching the intensity of the radiation of a given field with the 3D characteristics of the target volume. Multiple beams of radiation are aimed at the tumor target from different directions. Each beam will "see" the target volume as a unique outline, depending upon the angle from which the target is viewed. The target will also present with unique depths based on the angle at which it is viewed [8]. The tumor will appear thicker in some parts of the field and thinner in other sectors. Both the outline of the tumor and the tumor thickness will be unique for each beam aimed at the target. In the case of IMRT, the intensity of the radiation delivered by each beam is not uniform as it matches the differing shape and thickness that the target volume presents to the corresponding beam [4]. Where the tumor is viewed as thicker, more radiation is delivered, and where it is thinner, less radiation is needed. The sum total of multiple modulated radiation beams that all intersect in the middle of the tumor form a cloud of radiation energy that closely matches the 3D characteristics of the target tumor volume. A target radiation dose is assigned to the tumor, while appropriate normal tissue dose constraints are also taken into account [3]. In order to arrive at the optimal treatment plan, IMRT software utilizes an iterative process to randomly change a part of the solution until the target dose goal is met as much as possible while taking the normal tissue dose constraints into account so that the final plan can no longer be improved upon [4, 26]. This process typically involves the trial of millions of potential configurations until the optimal solution or plan is found.

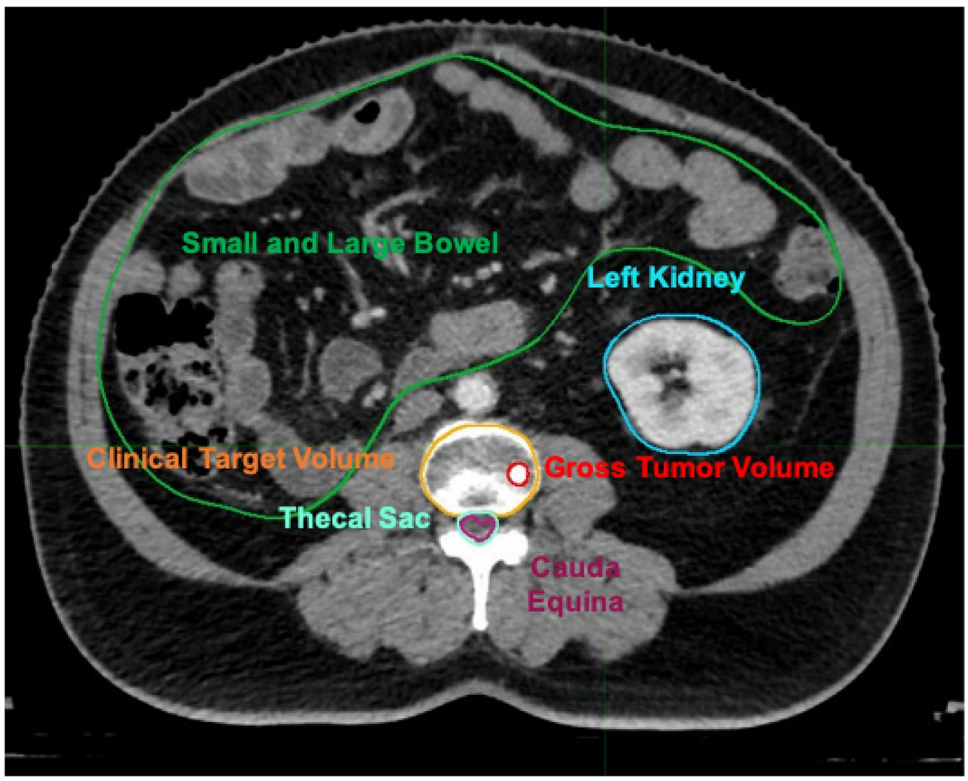

Fig. 1 Example of a spinal metastasis treatment volume. Anatomical depiction of an L3 spinal metastasis and surrounding structures on planning CT scan taken at simulation. The gross tumor volume (GTV) and clinical target volume (CTV) depict the targets of radiation therapy, while the remaining structures represent nearby organs at risk (OAR)

Because IMRT is able to reduce the dose of radiation that goes to normal tissues, it often allows for the escalation of dose within the target, subsequently increasing the probability of tumor control [27–29]. IMRT refers to radiation treatment that utilizes more conventional dose and fractionation regimens which are typically 1.8–2 Gy per fraction [4].

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) refers to radiotherapy that utilizes high dose per fraction radiation in two to five fractions [30]. It may also be referred to as stereotactic ablative body radiotherapy (SABR) [31]. When the entire course of treatment is given in a single fraction, it is referred to as stereotactic radiosurgery (SRS) [21]. Because SBRT if given with very large doses of radiation delivered per fraction, the BED of SBRT is quite high [32]. SBRT is delivered using the same technique as IMRT, which is necessary to minimize the dose delivered to normal tissues. 3D imaging, such as cone beam CT imaging, and more recently MRI scans are incorporated into treatment delivery to increase the precision of treatment and allow for the use of very tight margins around the target volume, minimizing the amount of normal tissue exposed to high-dose radiation [8, 32]. The high BED of SBRT provides for a greater probability of durable tumor control and is more ablative than conventionally fractionated radiation [33, 34]. However, SBRT is best utilized for smaller and more discrete targets because the normal tissue doses must be carefully controlled. Therefore, SBRT is often used to treat brain metastases, lung tumors, spine tumors, liver tumors, and discrete tumors in the abdomen, pelvis, and bone.

In the lung, SBRT has been shown to provide cure rates of early-stage lung cancer that are comparable to surgical resection [35–37]. Similarly, very high rates of tumor control have been observed when treating liver and spine lesions (see Tables 1 and 2) [33, 38, 39, 40•, 41–43]. SBRT is also frequently used when there is a need to reirradiate a previously treated tumor [44–46]. High BED treatment is often necessary to defeat tumors that have proven resistant to a prior course of radiation, and SBRT can limit the amount of dose delivered to normal tissues that may have been previously radiated and are resultantly less tolerant to radiation [21]. This is true especially in the setting of reirradiation of spinal metastases, where critical organs such as the spinal cord are only a few millimeters away [44].

Proton Beam Radiation Therapy

Proton beam radiation therapy (PBRT) is a highly specialized technology that utilizes protons rather than X-ray photons to deliver high precision radiation [5]. Photons or X-rays are quantum packets of energy and have no mass. Protons, on the other hand, are charged particles formed from hydrogen atoms. When a hydrogen atom is stripped of its orbiting electron, the result is a positively charged proton [2]. Protons can accelerate to very high velocities and penetrate into tissue to certain depths [2]. Because of their positive charge, protons can be manipulated in magnetic fields and directed at targets within patients with high precision. Since protons have mass, they acquire kinetic energy when accelerated. As they interact with atoms within a patient, they lose their kinetic energy, and when that energy is depleted, they stop and, beyond that point, provide no radiation dose within the patient. This phenomenon is referred to as the Bragg peak (Fig. 2) [6]. As protons slow down, they releases their energy very quickly, and the radiation dose they deliver will go from 100% to zero in a short span of 2 to 3 mm. Unlike photon-based treatment, with proton treatment, there is no exit dose or radiation that extends far beyond the depth of the target (Fig. 3) [5, 6]. In the case of photon treatment, there is always radiation dose that travels beyond the target, exposing normal tissue beyond the target volume to radiation. Hence, proton beam treatment

Table 1 Selected studies on liver stereotactic body radiation therapy

First author	Year	Sample size	Dose	Follow-up (months)	Local control	Overall survival	Toxicity
Rusthoven	2009	47	36–60 Gy/3	16	95% (1 year)	30% (2 years)	2% grade 3
Scorsetti	2018	61	75 Gy/3	72	94% (3 years)	18% (5 years)	2% grade 3
Folkert	2021	33	35–40 Gy/1	26	96% (4 years)	82% (2 years)	No grade 3

Table 2 Selected studies on lung stereotactic body radiation therapy

First author	Year	Sample size	Dose	Follow-up (months)	Local control	Overall survival
Miyakawa	2017	71	48–52 Gy/4	44	85% (5 years)	65% (5 years)
Nyman	2016	102	66 Gy/3	37	86% (3 years)	54% (3 years)
Sun	2018	65	50 Gy/4	86	92% (7 years)	48% (7 years)
Bezjak	2019	102	57.5 Gy/5 or 60 Gy/5	38	88–89% (2 years)	68–73% (2 years)

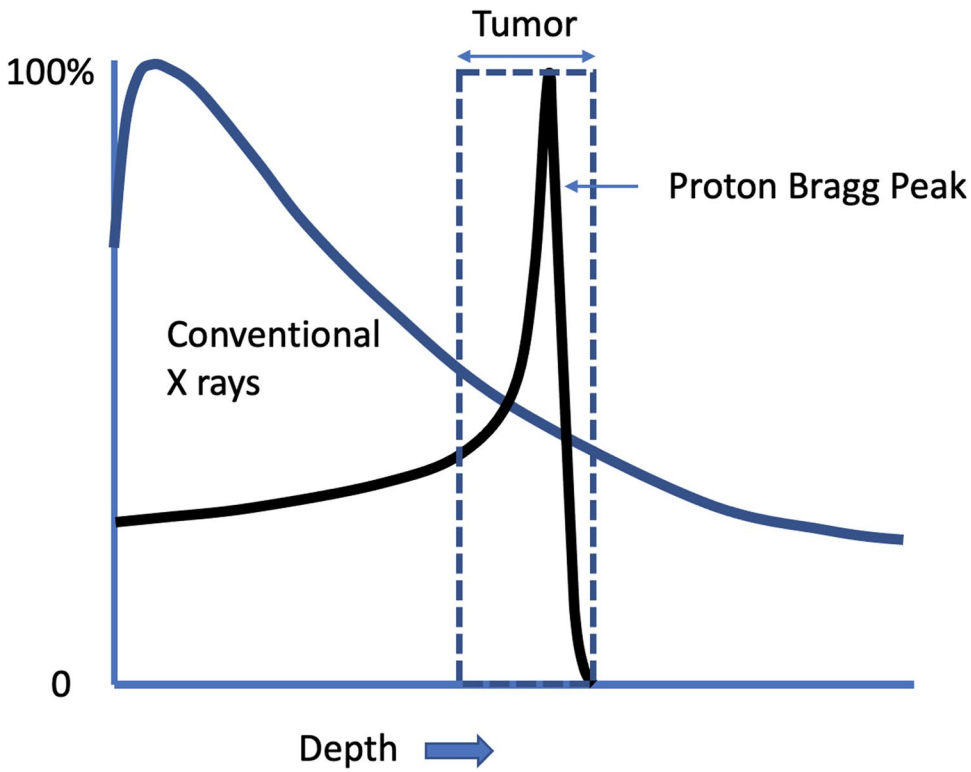

Fig. 2 Bragg peak effect diagram. Graphical depiction of the Bragg peak effect of protons. Protons acquire kinetic energy when accelerated. As they interact with atoms, they quickly lose their kinetic energy, and when that energy is depleted, they stop and, beyond that point, provide no radiation dose

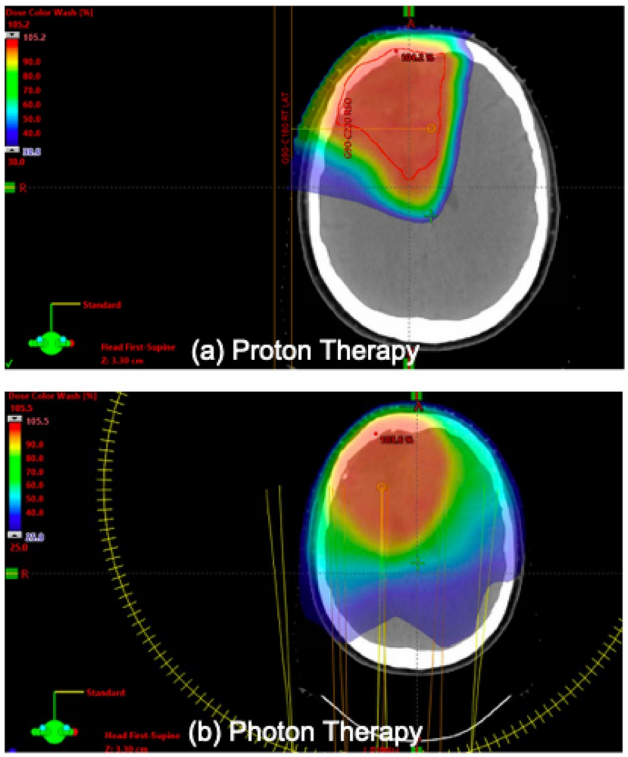

Fig. 3 Comparison of dose distribution map of **a** proton therapy versus **b** photon therapy. Unlike photon-based treatment, with proton treatment, there is no exit dose or radiation that extends far beyond the depth of the target

is extremely useful in the treatment of growing children, whose organs are sensitive to even low-dose radiation [47]. Because of the high precision of proton beam therapy given the Bragg peak effect, proton beam therapy is very susceptible to small errors in positioning and setup and changes in the patient's body [48]. Even a small change in the path length that a proton travels to reach the tumor can result in part of a tumor receiving no radiation at all or overdosing of a critical nearby structure. Proton beam therapy is not widely available and requires superconducting magnets to direct proton beams, an expensive technology with limited equipped facilities at the moment. Proton beams are radiobiologically more complex than photons, but only slightly more potent and offer similar rates of tumor control. By convention, photon beam doses are converted to proton doses by multiplying them by a factor of 1.1 [5].

Conclusion

With respect to radiation therapy, the therapeutic ratio is a quantitative way of evaluating the probability of tumor control against the probability of toxicity [6]. Technologic advances such as intensity modulation, image guidance, and proton beam therapy have improved the therapeutic ratio by reducing the overall volume of radiated tissue, including radiation dose to surrounding normal tissue, while allowing for dose intensification within the target tumor volume.

Declarations

Conflict of Interest Yoshiya Yamada has financial relationships with Varian Medical Systems, Brainlab, and Vision RT as a consultant. Kaitlyn Lapen declares no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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