Revolutionizing Cancer Care: The Technological Progress of External Beam Radiation Therapy

Abstract

External beam radiation therapy (EBRT) has evolved from rudimentary low-energy machines in the late 1800s to sophisticated, high-energy systems used today. Initially limited by low penetration and high damage to surrounding tissues, early kilovoltage units could only treat superficial cancers. Technological breakthroughs in the mid-20th century introduced megavoltage machines like linear accelerators, which enhanced treatment precision and reduced skin damage. The development of stereotactic radiotherapy (SRT) provided highly accurate tumor targeting, minimizing exposure to healthy tissue. Innovations such as mini-beam radiation therapy (MBRT) and proton mini-beam radiation therapy (pMBRT) have further advanced EBRT, offering spatial dose fractionation and exceptional tissue-sparing properties. These techniques have shown promise, especially in treating complex cases such as brain metastases, by improving tumor control and reducing side effects. The continuous refinement of EBRT, incorporating imaging and beam modification technologies, reflects a commitment to enhancing treatment outcomes and patient quality of life in oncology. This paper aims to discuss how technological advancements in EBRT have revolutionized cancer treatment by offering more therapeutic options, reducing radiotoxicity to surrounding healthy tissue, and enabling more precise targeting of tumors.

Revolutionizing Cancer Care: The Technological Progress of External Beam Radiation Therapy

Introduction

External beam radiation therapy (EBRT) represents a cornerstone in treating various cancers, employing advanced technology to deliver precise doses of radiation to tumors.[1] This field has evolved significantly over the decades, driven by technological innovations to enhance treatment effectiveness and safety.[1-3] The advancements in EBRT have transformed cancer treatment, evolving from the primitive low-energy machines of the late 1800s to modern high-energy linear accelerators.[1] Techniques such as stereotactic radiotherapy (SRT), mini-beam radiation therapy (MBRT), and proton mini-beam radiation therapy (pMBRT) have further revolutionized the field.[1]

SRT has introduced a highly precise method for targeting tumors, significantly reducing exposure to healthy tissues.[4] MBRT and pMBRT offer innovative approaches, optimizing dose distribution and minimizing side effects.[4,5] Understanding the historical development and integration of these advanced techniques is crucial for appreciating the sophisticated technologies and methodologies supporting contemporary radiation therapy and the ongoing pursuit of improved patient outcomes.[1,2] This paper aims to discuss how technological advancements in EBRT have revolutionized cancer treatment by offering more therapeutic options, reducing radiotoxicity to surrounding healthy tissue, and enabling more precise targeting of tumors.

History of External Beam Radiation Therapy

EBRT uses advanced technology to administer radiation for cancer treatment.[1] The equipment has become increasingly sophisticated over the years, requiring radiation therapists to

remain updated on technological innovations.[1] In the late 1800s, early machines had low energy outputs, restricting their ability to treat various cancers and requiring more manual operation.[1] Advancements in mechanical and computer technology for the simulation, planning, and delivery of EBRT have significantly improved both the dose delivered and the duration of treatment.[1]

Previously, simpler equipment could not conform to the tumor volume, limiting the prescribed dose due to large treatment fields.[1] The introduction of higher-energy units and improved computer systems enhanced treatment precision and efficiency, but increased the amount of radiation delivered.[1,3] Initially, EBRT was based on 2D imaging and bony anatomy, with early imaging limitations resulting in large field sizes and uneven dose distribution.[1]

With the advancement of CT imaging, 3-D planning for conformal radiation therapy began.[1] The shift from 2-D techniques to advanced treatments like intensity-modulated radiation therapy (IMRT), SRT, and particle therapy allowed for higher doses to be delivered to the tumor.[1] This also helped reduce radiation exposure to surrounding healthy tissue (see **Figure 1)**.[1] The capabilities of modern radiation therapy have significantly expanded due to advances in energy ranges, machine designs, and imaging technologies.[1-3]

Early EBRT equipment operated within the kilovoltage energy range, significantly limiting treatment.[1] Low-energy units, such as superficial machines (40-150 kV) introduced in 1896, could only treat cancers up to 2 cm deep due to limited beam penetration.[1] Orthovoltage machines (200-300 kV), introduced in 1923, had slightly higher energy levels but required manual adjustments to enhance radiation intensity.[1] These low-energy units often caused higher doses to surrounding tissues due to scattering, and their ability to control tumors was insufficient without harming healthy tissue.[1,3]

Medical physicists have developed higher-energy radiation therapy technology capable of deeper tissue penetration to improve tumor control while protecting the surrounding healthy tissue.[1,4-6] A major challenge before the 1950s-60s was producing adequate voltage with conventional transformers.[1] This led to the development of megavoltage treatment units, like linear accelerators, which utilize microwave power sources (magnetrons or klystrons) to accelerate electrons.[1] These high-energy machines not only treated a wider range of tumors but also reduced damage to the skin compared to earlier kilovoltage units.[1,4-6]

Dr. Henry Kaplan pioneered the medical use of linear accelerators in the late 1940s, leading to their clinical application in 1953.[1] Early models had limited gantry rotation (120 degrees) and lower voltage (8 MV) compared to modern machines (up to 25 MV).[1] By 1961, Varian introduced gantries with 360-degree rotation, improving dose delivery.[1] These early high-energy machines were structurally robust but less precise than current models.[1] With advanced technology and capabilities, today's linear accelerators offer a more comprehensive energy range (4 to 22 MeV for electrons and 6 to 25 MV for photons).[1]

Proton therapy, designed for treating heavy charged particles, emerged in clinical settings alongside linear accelerators starting in 1954.[1] Over the following decades, computers were integrated into proton treatment systems, enabling significant reductions in exit radiation doses.[1] This feature is particularly beneficial for minimizing long-term side effects in pediatric cancer patients.[1] Protons are generated by an ion source which removes electrons from hydrogen gas and are accelerated using cyclotrons or synchrotrons.[1] While most proton therapy facilities are extensive, compact technologies are being developed to enhance accessibility.[1]

Cobalt-60 (Co-60) is one of the most widely used radioactive sources in radiation therapy devices.[1] These machines, which have been utilized in EBRT for decades alongside linear

accelerators, have a simpler design.[1] Co-60 undergoes beta decay to become nickel-60, emitting photons with an average energy of 1.25 MeV.[1] While Co-60 machines are still used in many low-income countries, their usage has declined due to newer technologies like the Gamma Knife, which advances Co-60 use in stereotactic radiosurgery.[1]

Introducing on-board imaging systems and advanced beam modification technologies has significantly enhanced EBRT.[1] In the 1990s, integrating CT into treatment planning improved tumor visualization and control while sparing healthy tissue through smaller fields.[1] Multileaf collimators (MLCs) allowed for more precise dose distributions, leading to intensity-modulated radiation therapy (IMRT).[1] Image-guided radiation therapy has improved beam alignment with techniques like cone-beam CT and magnetic resonance imaging, facilitating better targeting of tumors, while 4D CT accounts for respiratory motion to ensure accurate delivery.[1] New patient alignment methods, such as optical monitoring and ultrasound, have also been implemented.[1]

Recent Advancements

The latest treatment machines enhance patient care with their innovative structural designs. Examples include helical tomotherapy, CyberKnife (Accuray Inc), MR imaging linear accelerators, and PET linear accelerators.[1] These modern devices build on principles from earlier technologies, offering improved functionality.[1] Their designs enable them to move around patients at various angles using fully robotic arms.[1] These advancements in EBRT have significantly broadened the treatment options for cancer patients.[1]

Helical tomotherapy machines, proposed in the 1990s and introduced for clinical use in 2003, deliver highly conformal dose distributions utilizing a binary MLC.[1] These machines feature a ring-based gantry design with a 6 MV linear accelerator capable of flattening filter-free beams.[1] The radiation source rotates around the patient while the treatment table moves

longitudinally through the gantry bore.[1] Unlike machines requiring multiple isocenters, tomotherapy units allow craniospinal irradiation to be treated with a single isocenter.[1]

During a discussion with a local radiologist (October 2024), the remarkable progress in radiation therapy technologies was highlighted, particularly emphasizing how quickly these advancements have occurred over a relatively short time frame. The radiologist also explained the specific treatment a patient receives is primarily determined by the type, stage, and location of their cancer. However, the variety of available techniques, lasers, and beams is exceptional, offering unprecedented flexibility in treatment planning. Looking ahead, he expressed optimism, noting how further advancements in these technologies will continue to enhance the precision and effectiveness of cancer treatments.

Mini-Beam Radiation Therapy

Radiation therapy (RT) is an essential cancer treatment, but its effectiveness is often constrained by the radiotoxicity it causes to healthy surrounding tissues.[3] Mini-beam irradiation is a cutting-edge radiotherapy technique using spatial fractionation to deliver higher doses to tumors while protecting surrounding healthy tissue, potentially enhancing tumor control and reducing side effects.[2,4-6] These methods focus on the differential responses of tumor and normal tissues to radiation rather than simply reducing the total dose to normal tissues.[2]

Initially developed with synchrotron radiation, it creates alternating high-dose (peaks) and low-dose (valleys) areas within the treatment area, showing normal brain tissue can tolerate high radiation levels without compromising tumor control.[2,4-6] Recent studies have demonstrated MBRT delaying tumor growth and improving survival, even with lower doses delivered to the valleys.[2,7] Research has also shown MBRT causes less brain damage, reduces skin toxicity, enhances tumor control, and leads to fewer long-term side effects compared to broad beam

irradiations.[7] However, the mechanisms behind this "mini-beam effect" are not fully understood, with theories suggesting roles for the immune system, the abscopal effect, and vascular responses.[6,7]

The technique typically employs slit widths of 0.2 to 1 mm, arranged in a metal structure with 1 to 4 mm spacing.[6] The mini-beam geometry is defined by the full width at half maximum (FWHM) and the center-to-center distance (CTC).[6] Adjusting these parameters significantly influences radiation toxicity.[6] For example, a 0.5 to 1 mm peak width shows no toxic effects, whereas a 3 mm peak width can cause severe reactions in animal models.[6] The CTC ideally remains constant, ranging from two to four times the FWHM.[6] At the same time, the peak-to-valley dose ratio (PVDR) is critical for biological responses, with effective results observed at PVDRs as low as 2.7 and up to 20.1 for various x-ray sources.[6]

In 2009, a research group developed a tungsten collimator capable of producing a beam 1000 μm wide.[8] This was the first collimator for mini-beam radiation research on a superficial x-ray machine.[8] As a result, the first MBRT collimator was developed to produce a megavoltage mini-beam on a linear accelerator.[8]

In 2017, the feasibility of mini-beam irradiation was evaluated using a small animal x-ray irradiation device, revealing this technique could be both affordable and easily implemented.[6] Effective mini-beam dose delivery requires a mini-beam collimator, which can be easily installed in x-ray systems.[6,8] However, the collimator must align with the source's divergence to ensure a sharp radiation pattern, complicating adjustments to the source-to-collimator distance (SCD) and the interchangeability of collimators across different devices.[6]

Testing various PVDRs is also crucial, as these variations significantly impact the mini-beam effect.[6,8] Common materials for collimators include tungsten and brass, with tungsten

being particularly favored for its high attenuation coefficient for x-rays, allowing for higher PVDR values.[6,8] Ultimately, controlling the FWHM, ctc, and PVDR is essential for preclinical studies of the mini-beam effect, helping clarify each parameter's influence.[6]

Proton Mini-Beam Radiation Therapy

Cancer metastases are a leading cause of cancer-related deaths and can occur in various cancer types.[3-5] They are frequently treated with radiotherapy, particularly SRT.[3,4] pMBRT is an innovative approach utilizing spatial dose fractionation.[4,7] When paired with SFRT, pMBRT provides unique advantages, such as no dose deposition beyond the Bragg peak and maintaining homogeneous dose distributions.[7] Compared to SRT, pMBRT may offer significant advantages for treating large metastases, thanks to its impressive ability to spare normal tissue while maintaining high tumor control rates, as demonstrated in preclinical studies.[7]

pMBRT treatments offer comparable tumor coverage to conventional stereotactic techniques while significantly reducing the integral dose to surrounding organs at risk.[4,7] Additionally, the enhanced standard tissue-sparing capability of mini-beams allows for treatment to be delivered with fewer fields and in a single fraction, all while adhering to normal tissue dose tolerances.[4,5] As a result, pMBRT is expected to improve the therapeutic index for treating metastases.[4,7]

Case Study

Brain metastases affect 10–30% of cancer patients, with the occurrence growing over the last twenty years.[5] The risk of developing additional brain metastases after initial treatment has also increased as technological advancements prolong patient survival.[5] Whole-brain radiotherapy (WBRT) is the standard form of treatment for patients with multiple brain metastases.[5] Unfortunately, recurrence is common despite successful treatment, requiring

whole-brain re-irradiation to alleviate symptoms.[5] However, repeat WBRT raises concerns over neurotoxicity and cognitive effects, stressing the need for safer, more effective re-irradiation strategies.[5]

While many studies have explored the benefits of SFRT in treating brain tumors, few have specifically investigated its potential as a re-irradiation strategy for brain metastases.[5] Researchers hypothesized MBRT could offer advantages over conventional uniform radiation, believing it could reduce treatment-related toxicity when used for re-irradiation following the initial WBRT.[5] A study focused on a mouse model was conducted to explore MBRT as a less toxic alternative to conventional WBRT.[5]

The study aimed to compare MBRT's safety profile to the conventional WBRT by evaluating the toxicity and biological effects of different radiation doses.[5] Three groups of healthy mice were exposed to various radiation protocols: a control group receiving 25 Gy of conventional uniform radiation and two experimental groups receiving MBRT at a low dose of 25 Gy and a high dose of 43 Gy (see **Figure 2)**.[5] The low-dose MBRT (25 Gy) group resulted in less body weight loss and better preservation of proliferative brain progenitor cells than conventional uniform radiation (25 Gy).[5] High-dose MBRT (43 Gy), however, led to significant radiation toxicity, emphasizing the critical role of proper dosing to minimize adverse side effects.[5]

This study faced several limitations, including no real-time imaging during radiation treatments, reliance on a single post-re-radiation assessment after five weeks, and using healthy mice.[5] The use of healthy mice didn’t fully account for the complexities of patients with brain metastases. Diseased subjects and human trials would need to be used in future studies to validate these findings and determine optimal dosing. Long-term research is also required to

properly evaluate the cognitive and neurological effects of MBRT over extended periods. Overall, the study offers preliminary evidence showing MBRT as a more tolerable re-irradiation option, potentially reducing systemic side effects and preserving cognitive function when administered with the correct dosage.

Conclusion

The historical and ongoing advancements in external beam radiation therapy underscore the remarkable progress in cancer treatment. From early kilovoltage units with limited capabilities to the emergence of megavoltage machines and innovative techniques such as SRT, MBRT, and pMBRT, each development has aimed to enhance tumor control while minimizing damage to healthy tissues. SRT has enabled precise targeting of tumors, improving outcomes with minimal side effects. MBRT, with its spatial dose fractionation, and pMBRT, known for its exceptional tissue-sparing properties, have further expanded treatment options, particularly for complex cases like brain metastases.

These improvements have broadened the applicability and precision of EBRT, offering hope and extended survival to patients worldwide. As research continues and new technologies emerge, the future of EBRT holds promise for even greater treatment effectiveness, safety, and patient quality of life. The lessons learned from past developments and the incorporation of cutting-edge techniques like SRT, MBRT, and pMBRT will continue to inform and inspire future innovations, ensuring EBRT stays at the forefront of cancer care.

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Figures

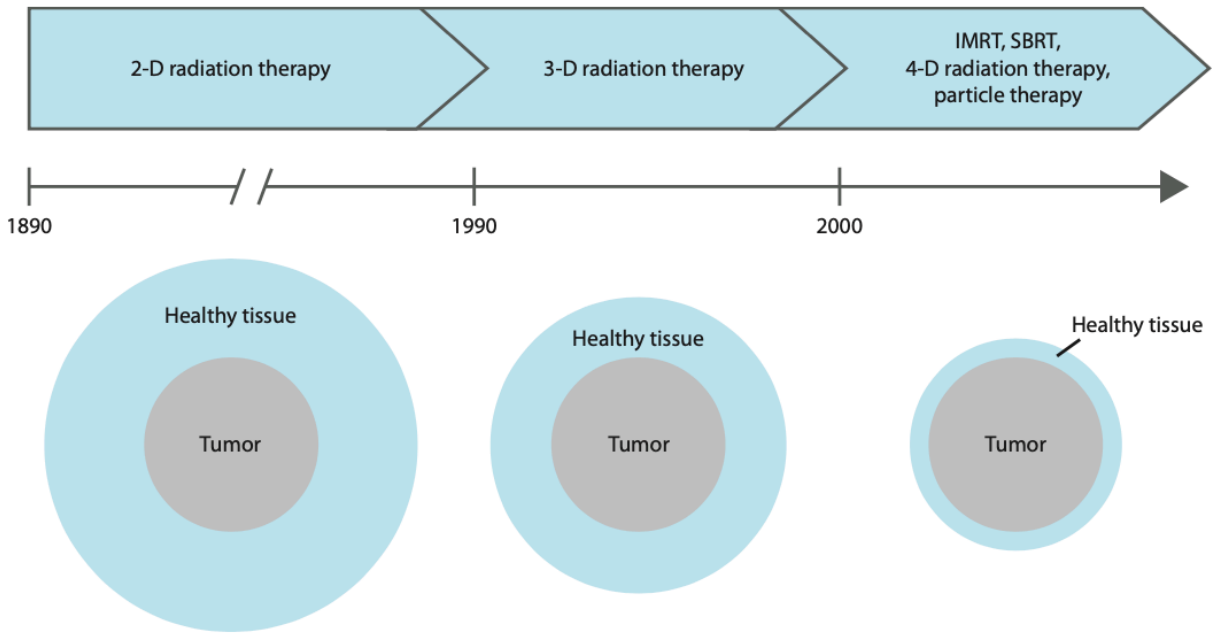

Figure 1. *Illustration depicting the evolution of modern radiation therapy to minimize the volume of healthy tissue being unnecessarily irradiated. Reprinted under the Creative Commons Attribution Non-Commercial 4.0 International License. Abbreviations: IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy. Image courtesy of:* Gomez S, Trad M. Evolution of external beam radiation therapy technology. *Radiat Therapist*. 2024;33(1):38-44. https://research-ebsco-com.libpublic3.library.isu.edu/linkprocessor/plink?id=e8212b04-b794-3871-85b6-237f57fff9b4. Accessed October 22, 2024

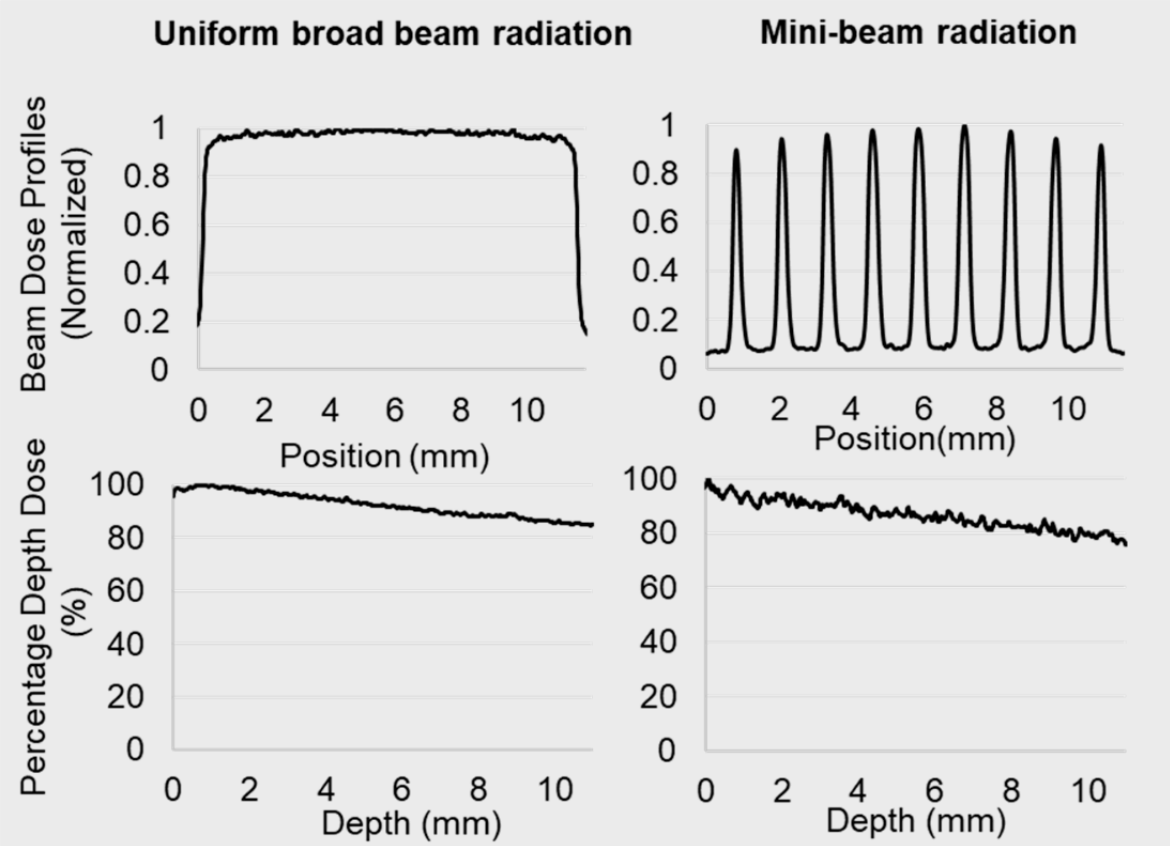

Figure 2. *MBRT dose profiles and percentage of depth dose measurements. Beam profiles and percentage depth dose (PDD) for the 25 Gy BBRT and the two MBRT treatments were measured by EBI-3 film calibrated against an ion chamber in large field conditions. The dose rate at the 5 mm tissue depth is 3.5 G / min for the mini-beam and 4.98 G / min for the broad beam radiation. Image courtesy of:* Yuan H, Rivera JN, Frank JE, Nagel J, Shen C, Chang SX. Mini-beam spatially fractionated radiation therapy for whole-brain re-irradiation—a pilot toxicity study in a healthy mouse model. *Radiat*. 2024;4(2):125-141. doi:10.3390/radiation4020010