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ОБЗОР
REVIEW

Shaping the future of radiotherapy: the role of electron beams and flash techniques

Mikhail A. Parshenkov ✉, Polina P. Skovorodko, Danila A. Petrusevich, Shagun N. Makaeva, Svetlana G. Osipova, Gumru R. Ibragimova, Alexandra O. Istyagina, Kristina A. Balaeva, Galina M. Rodionova

First Moscow State Medical University (Sechenov University), *Moscow, Russian Federation*
✉misjakj@gmail.com

Abstract. *Relevance.* Radiation therapy (RT) remains a cornerstone of oncology, offering targeted treatment for various cancers. With its roots tracing back to the discovery of X-rays by Wilhelm Röntgen and radium research by Marie Curie, RT has evolved into a sophisticated field encompassing a range of techniques. However, the rising global cancer burden highlights the need for continuous advancements to enhance efficacy while minimizing collateral damage. Traditional modalities such as X-rays and gamma rays have established their role in cancer treatment, yet they often lead to unintended damage to healthy tissues. Electron therapy has emerged as a promising alternative, leveraging distinct dosimetric properties that enable precise targeting with limited penetration depth. Low-energy electron beams are ideal for superficial tumors, while Very High-Energy Electrons (VHEEs) extend the reach to deep-seated tumors, rivalling proton and heavy-ion therapies. Furthermore, the FLASH effect — a phenomenon reducing healthy tissue toxicity at ultra-high dose rates, offers a breakthrough in electron therapy, improving patient quality of life. Despite these advancements, challenges persist. Limited penetration depth, secondary radiation from bremsstrahlung, and complexities in dose delivery systems constrain broader clinical adoption. Moreover, unresolved biological uncertainties, such as variability in relative biological effectiveness (RBE), necessitate further research. This review explores the historical evolution, unique benefits, and limitations of electron therapy compared to traditional modalities. It highlights advancements like VHEEs, FLASH therapy, and hybrid approaches, while addressing technological challenges and the future potential of electron beams in oncology. *Conclusion.* Integrated with recent technological breakthroughs, electron therapy may redefine the future of radiotherapy by offering safer, more precise, and individualized cancer treatment strategies.

Keywords: radiation therapy, very high-energy electrons, accelerators, ultra-high dose rate FLASH therapy, oncology

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Introduction

Radiation therapy (RT), one of the fundamental methods for cancer treatment worldwide, has a rich history spanning over 130 years (Figure 1) [1]. Wilhelm Röntgen's discovery of X-rays in 1895 marked a revolutionary turning point in medicine, enabling the use of ionising radiation to treat various types of malignant tumours. Building on this foundation, Marie Curie's pioneering research on Radium [2, 3], for which she received a Nobel Prize, laid the groundwork for modern radiotherapy, making it a critical component in oncology and helping to save countless lives. Today, radiotherapy is supported by a multidisciplinary team of radiation oncologists, medical physicists, dosimetrists, and radiotherapists, all working collaboratively to ensure precise planning and delivery of treatment.

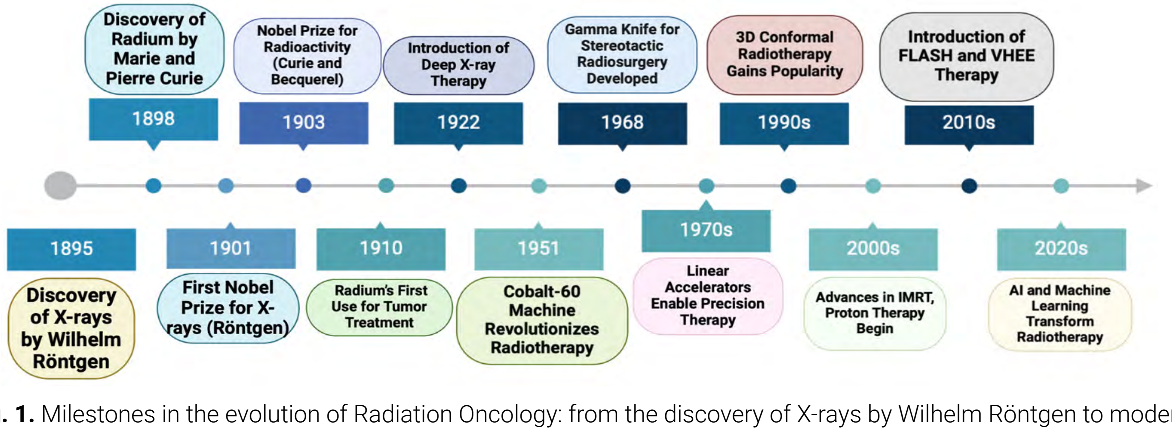

Fig. 1. Milestones in the evolution of Radiation Oncology: from the discovery of X-rays by Wilhelm Röntgen to modern advancements like FLASH and VHEE therapy

The field faces growing challenges as cancer cases are projected to increase by 77% by 2050, according to the World Health Organization [4]. This anticipated rise underscores the pressing need for continuous advancements in radiation therapy to meet the increasing demand for effective cancer treatment.

Radiation therapy has become an indispensable modality in modern oncology, serving both as a standalone treatment for malignant neoplasms (MN) and as an adjunct to other therapeutic approaches, including surgical interventions, chemotherapy, targeted molecular therapies, and immunotherapy [5]. The choice of radiation therapy method depends on various factors, such as the type, localization, and stage of cancer, highlighting the necessity of personalized treatment strategies for each patient.

Among its numerous applications, radiation therapy has shown particular efficacy in the treatment of breast cancer, where it plays a central role in both curative and palliative settings [6]. Techniques such as three-dimensional conformal radiation therapy (3D CRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) are widely employed [7–9]. Their effectiveness varies depending on tumor location and stage, with VMAT often preferred for left-sided breast cancer to minimize cardiac and pulmonary toxicity, while 3D CRT remains the method of choice for right-sided cases to reduce myocardial exposure [10]. Additionally, hypofractionation schedules, which reduce the overall treatment duration, have been increasingly adopted to improve patient convenience while maintaining therapeutic efficacy [11].

Radiation delivery methods are broadly classified into external beam radiation therapy (EBRT), brachytherapy, and systemic radiation. EBRT utilizes high-energy beams such as X-rays, gamma rays, or particles like electrons and protons, targeting tumors with high precision through advanced imaging and planning technologies [12]. On the other hand, brachytherapy involves placing radioactive sources directly within or adjacent to the tumor, allowing for localized dose escalation while minimizing exposure to surrounding healthy tissues [13]. These approaches, combined with emerging techniques such as adaptive radiation therapy and proton therapy, aim to enhance the therapeutic index by achieving higher tumor control rates with reduced toxicity to normal tissues (Figure 2).

Recent advancements in radiation oncology have not only refined traditional approaches but have also integrated multi-modality treatment strategies. For instance, the combination of different radiation techniques with systemic therapies has enabled the targeting of radioresistant tumors, increasing the likelihood of achieving durable local control [14]. Furthermore, advanced imaging and treatment planning systems have improved dose conformity, enabling clinicians to optimize radiation delivery while protecting critical structures and minimizing long-term side effects [15].

However, despite the crucial position that RT occupies in the treatment of multiple cancers, the effects of ionizing radiation on the body are complex and affect biological structures at the cellular, molecular and other levels. Conventional methods of irradiation, including X-ray and gamma therapy, although effective, often result in collateral damage to healthy tissue, highlighting the need to develop better approaches that maintain therapeutic efficacy while minimizing harm.

Electron therapy has emerged as a promising alternative in this regard, offering distinct physical properties that allow for more targeted radiation delivery with reduced penetration depth. This feature enables electron therapy to be highly effective for treating tumors located near the skin surface or in shallow tissue areas [16], making it less likely to impact deeper organs and structures. Unlike photon-based radiotherapy, which can penetrate deeply and affect both the tumor and surrounding tissue, electron therapy's limited depth of action presents significant potential for reducing treatment-related side effects [17, 18].

Recent advances have broadened the potential of electron therapy. *Very High-Energy Electrons* (VHEEs, 100–250 MeV) now show promise for treating deep-seated tumors, approaching the precision of proton and carbon ion therapies while offering a more accessible and cost-effective alternative [19]. A key advantage of electron beams is their compatibility with the FLASH effect — a phenomenon in which ultra-high dose rates reduce toxicity to healthy tissue without

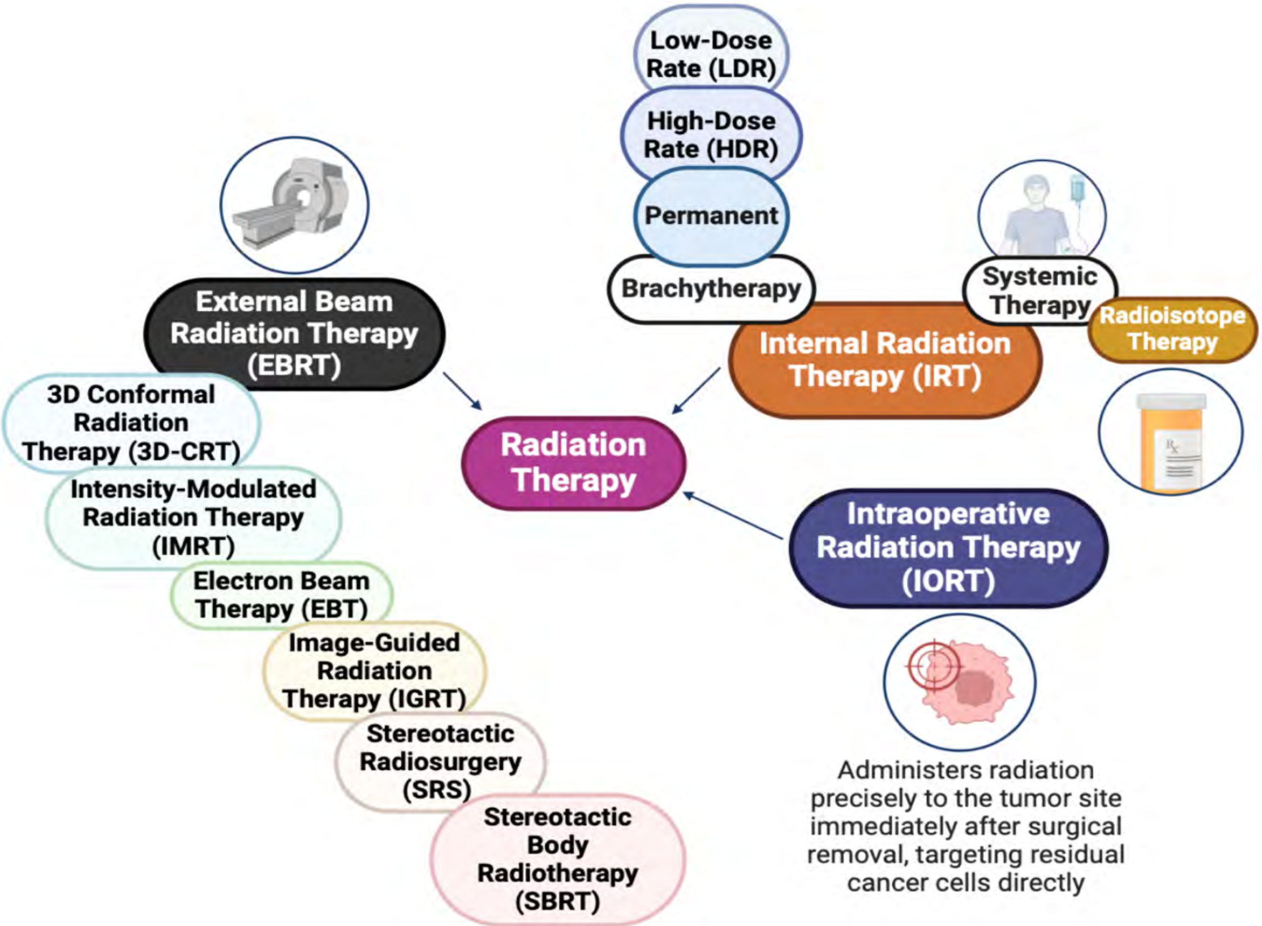

Fig. 2. Overview of modern Radiation Therapy Techniques and their applications

sacrificing tumor control [20]. By harnessing FLASH, electron therapy may dramatically reduce side effects and improve patients' quality of life.

We explore the potential of electron therapy within the broader scope of radiotherapy, emphasizing its unique benefits, limitations, and its comparison with other radiation types, such as X-rays and gamma rays. This paper also addresses current technological challenges and examines the promise of advanced techniques, such as the FLASH effect and *Very High-Energy Electrons*, in establishing electron therapy as a standalone and safer modality in radiation treatment. By offering a comprehensive overview of its advantages, limitations, and areas ripe for further research, this review aims to support advancements in oncology to enhance radiotherapy outcomes for patients.

Fundamental principles of radiation therapy

Radiation therapy is a cornerstone of oncology, utilizing high-energy particles or waves [21]. The targeted damage induces cell death in malignant tissues, making radiation therapy an effective strategy for treating a wide range of cancers. The success of this approach depends on several factors, including the type of radiation, linear energy transfer (LET), total dose, fractionation schedules, and the radiosensitivity of tumor cells [22].

A critical determinant of the biological effectiveness of radiation therapy is linear energy transfer (LET), which measures the energy deposited by radiation per unit distance travelled in tissue [23]. The High-LET radiation, such as alpha particles or neutrons, creates dense ionization tracks, resulting in more severe macromolecular damage and increased cell lethality compared to low-LET radiation like X-rays or gamma rays [24]. This heightened damage includes double-strand breaks (DSBs) in DNA [25], a pivotal factor in inducing apoptosis, necrosis, or cellular senescence. Also, The High-LET radiation could engage specific DNA repair pathways, with non-homologous end-joining (NHEJ) being particularly critical [24]. Notably, defects in NHEJ pathways lead to heightened radiosensitivity across various LET ranges, emphasizing the central role of repair mechanisms in determining radiation-induced cell fate (Figure 3) [25, 26].

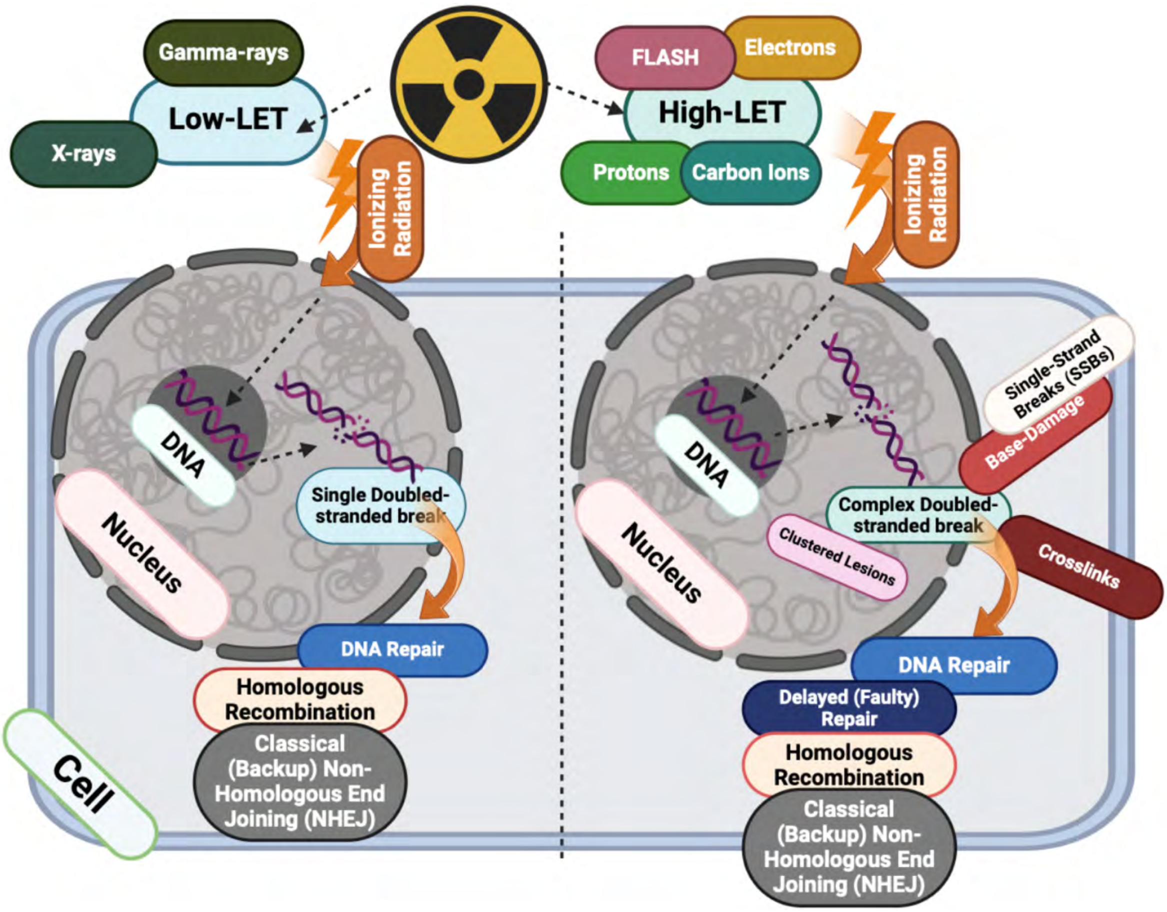

Fig. 3. Comparison of DNA damage and repair mechanisms induced by low-LET and high-LET radiation

The relationship between LET and relative biological effectiveness (RBE) is intricate. While the high-LET radiation is generally associated with increased RBE, this relationship varies depending on radiation quality, cellular characteristics, and biological endpoints under investigation. Recent studies highlight inconsistencies in how LET is defined and averaged across the literature, potentially undermining RBE modelling and its clinical translation [27]. Resolving these inconsistencies is paramount to enhancing the precision of treatment planning and improving therapeutic outcomes.

Beyond DNA damage, the biological effects of LET encompass secondary mechanisms such as oxidative stress and bystander effects. Oxidative stress, driven by reactive oxygen species (ROS), exacerbates cellular damage, while bystander signalling propagates radiation effects to neighbouring cells, influencing both tumor control and normal tissue toxicity (Fig. 4) [28–30]. Understanding these mechanisms is particularly critical for advancing novel radiation modalities, including proton therapy and heavy-ion radiation, which inherently rely on the interplay between LET and biological response.

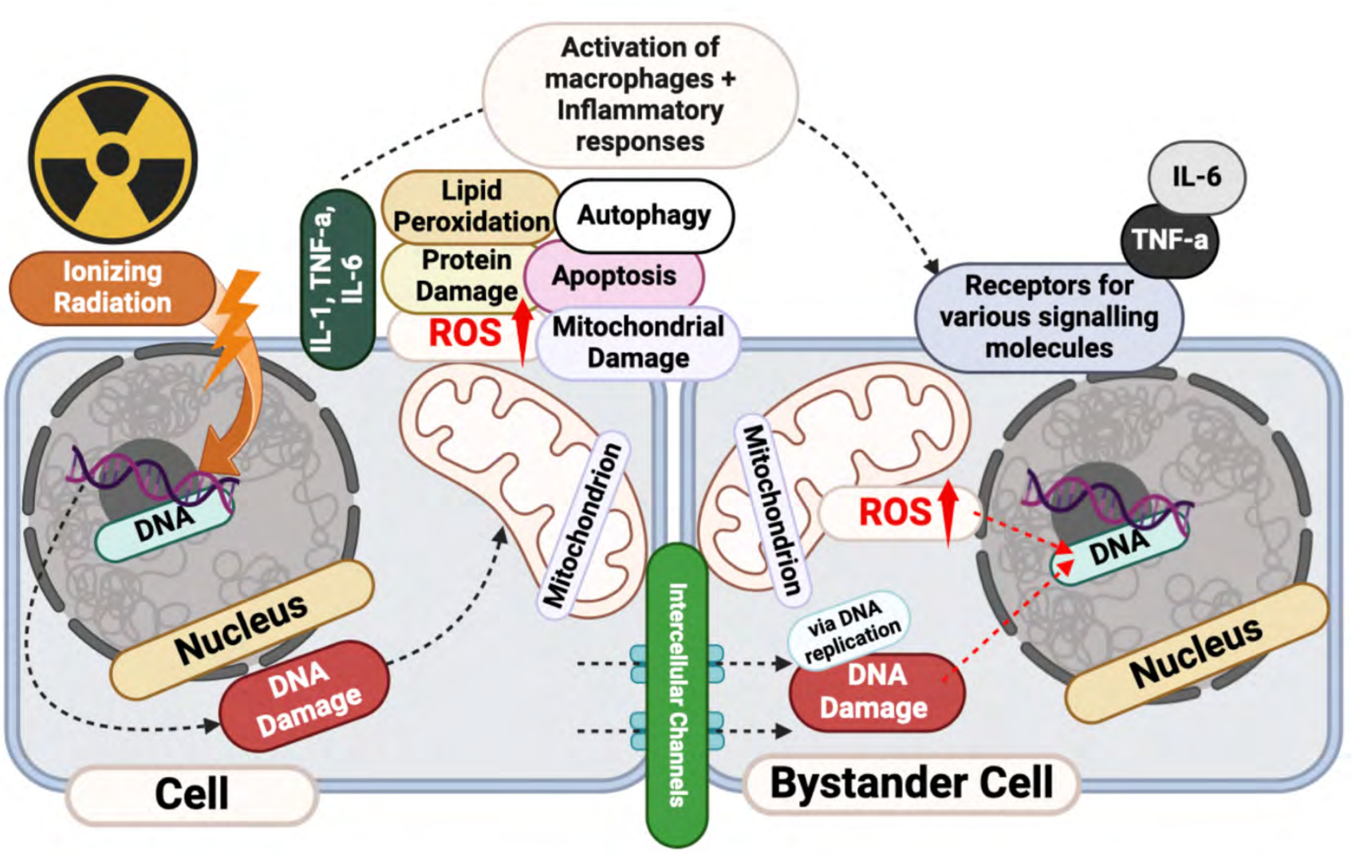

Fig. 4. Mechanisms of Radiation-induced cellular and Bystander effects

By integrating these insights, radiation therapy continues to advance as a precise and adaptable treatment modality in oncology. Nevertheless, challenges persist, including the variability of RBE predictions and the absence of universally accepted LET parameters. These hurdles underscore the need for ongoing research to refine biological models and optimize clinical application, paving the way for more effective and individualized cancer treatments.

Electron Irradiation

Electron irradiation presents significant potential in radiation oncology due to its distinct physical properties, particularly penetration depth and scattering patterns [31]. These properties are critical for optimizing electron-based treatments, especially in scenarios where precision is required to target tumors while preserving adjacent healthy tissues.

The penetration depth of electron beams is highly dependent on their energy and the atomic composition of the irradiated material [32]. Low-energy electron beams (6–20 MeV) are well-suited for treating superficial malignancies, as their limited penetration depth ensures dose delivery primarily to the skin and shallow tissues, sparing underlying structures [33]. On the other hand, *Very High-Energy Electrons* (VHEEs), with energies exceeding 100 MeV, provide the capability to treat tumors located at depths of 5–15 cm while maintaining dose conformity even in heterogeneous tissues such as the lungs and bones [34, 35]. These properties position VHEEs as a potential alternative to photon and proton therapies for certain clinical applications (Figure 5).

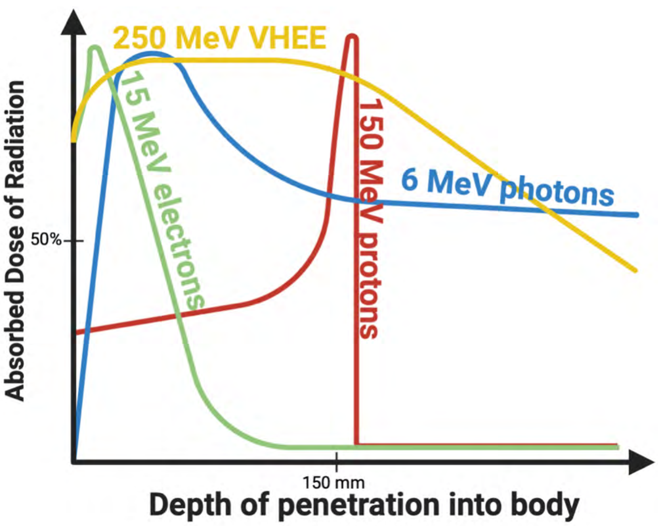

Fig. 5. Theoretical depth-dose distribution of radiation in water for various particle beams. The graph illustrates the absorbed dose of radiation as a function of penetration depth for different particle types, including 6 MeV photons, 15 MeV electrons, 150 MeV protons, and 250 MeV Very High-Energy Electrons (VHEEs)

Recent innovations, such as FLASH radiotherapy, have further expanded the potential of electron beams. FLASH therapy involves delivering ultra-high dose rates (>40 Gy/s), which have been shown to reduce normal tissue toxicity while preserving tumor control [36]. Although most FLASH studies in medical literature have focused on low-energy electrons, VHEEs could extend this modality to deeper-seated tumors. The precise mechanisms underlying the FLASH effect remain under investigation, with current hypotheses suggesting reduced oxygenation and suppression of reactive oxygen species as key factors [37].

Electron scattering is central to treatment planning, as elastic, inelastic, and bremsstrahlung interactions shape dose distribution, especially in anatomically complex regions [38, 39]. Monte Carlo simulations remain the gold standard for modeling these effects, accurately predicting energy deposition, range straggling, and lateral spread across media [40]. Notably, VHEE beams exhibit a stable, narrow profile at depth, delivering more uniform doses than photons in heterogeneous tissues [41]. Fermi-Eyges models, closely aligned with Monte Carlo data, further enable faster, high-precision calculations for VHEE therapy [42].

Advances in beam delivery systems, such as active scanning techniques and pencil beam scanning, have significantly enhanced the precision of electron therapy [43]. These technologies enable highly focused dose delivery, reducing exposure to surrounding tissues and accommodating complex tumor geometries. For example, a 160 MeV laser-wakefield accelerated electron beam has been focused to a 2.3 × 2.6 mm^2 spot, demonstrating the feasibility of stereotactic radiotherapy with sub-millimeter precision [41, 43]. Furthermore, integrating Monte Carlo methods with imaging modalities like dual-energy CT has refined treatment planning, improving the accuracy of stopping power ratios and dose predictions [44].

Combining different electron beam energies offers additional flexibility in treatment. For instance, mixed-energy beams can effectively expand the treatment region while maintaining steep dose “fall-offs”, enabling the precise targeting of irregularly shaped tumors [45]. This versatility highlights the adaptability of electron therapy for a wide range of clinical scenarios and emphasizes the different situation of use.

Gamma Irradiation

Another approach we would like to focus on is gamma irradiation. Gamma radiation, a high-energy form of electromagnetic radiation, stands out for its exceptional penetration capabilities, making it indispensable in radiotherapy and other applications [46]. Its uncharged, high-energy photons enable gamma rays to deeply penetrate matter, interact with tissues via ionization, and cause excitation at the atomic level [47]. These interactions underlie gamma radiation's ability to inactivate pathogens, extend food shelf-life, and perform critical roles in medical and industrial applications. In radiotherapy, gamma rays interact primarily through the Compton effect, leading to ionization and subsequent biological effects, including DNA damage [48].

Typically, gamma rays are generated through radioactive decay, nuclear fission, or advanced particle accelerators [49]. $Cobalt^{60}$ and $Cesium^{137}$ are among the most widely used isotopes, offering reliable gamma ray emission for therapeutic and research purposes [50]. These rays exhibit wavelengths ranging from approximately 0.25 to 0.005 angstroms, with energy levels spanning tens of thousands to several million electronvolts [51]. Due to their high energy, effective shielding using dense materials like lead or concrete is essential in clinical and, for example, industrial settings.

Additionally, gamma radiation is integral to radiosurgical techniques, with *the Gamma Knife* exemplifying its precision and effectiveness in treating localized conditions (Figure 6) [52]. This non-invasive method uses 201 Cobalt*60* sources to deliver focused beams, achieving high doses at targeted lesions while sparing adjacent healthy tissue [53]. *The Gamma Knife* has demonstrated success in managing arteriovenous malformations (AVMs) and inoperable brain tumors, with studies linking biologically effective doses to higher obliteration rates [54]. Recent advancements, such as frameless *Gamma Knife* radiosurgery, have enhanced patient experience, enabling fractionation without compromising spatial resolution [55]. These developments underscore gamma radiation's role in advancing neurosurgical outcomes.

Despite its extensive applications, the effective and safe use of gamma radiation relies on accurate dosimetry and individualized treatment planning [56]. Dosimetric verification methods, including gamma analysis, are vital for ensuring precise dose delivery in treatments like *Gamma Knife* radiosurgery. However, standard

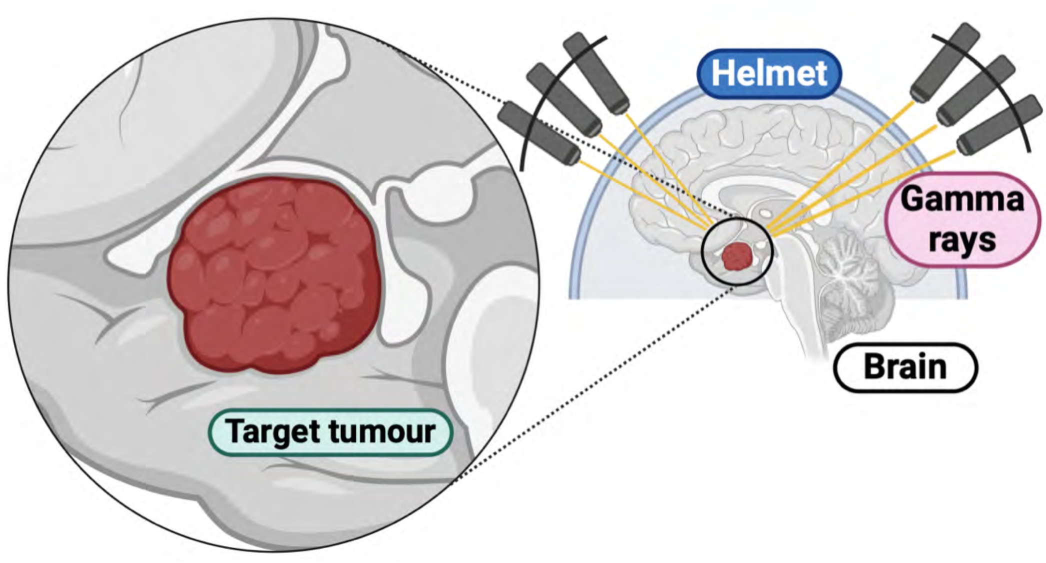

Fig. 6. Schematic representation of *Gamma Knife* radiosurgery. The diagram illustrates the precise targeting of a brain tumor (target tumour) using converging gamma rays, delivered through a specialized helmet. The focused radiation beams spare the surrounding healthy brain tissue, demonstrating the non-invasive and localized nature of the treatment

activity prescriptions often fail to account for individual patient differences, necessitating advancements in personalized dosimetry techniques. Challenges such as non-standardized protocols and the complexity of dose distribution modelling require further research and technical innovation to optimize patient outcomes.

Recent innovations, such as “mini-beam” collimator designs, have improved gamma-based dose conformity, allowing for narrower beams with high peak-to-valley dose ratios. Techniques like volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) further enhance precision by modulating collimator positioning, dose rates, and gantry speeds [57]. These advancements minimize radiation exposure to surrounding tissues, reducing side effects and enhancing treatment outcomes.

Finally, it is important to consider that gamma radiation’s biological efficacy is enhanced by its linear energy transfer, especially in radiosurgical applications. While low-LET radiation like gamma rays primarily causes single-strand DNA breaks, high-LET radiation, including α-particles and heavy ions, induces complex DNA damage such as clustered lesions and multiple double-strand breaks (DSBs) [58]. These DSBs activate homologous recombination repair pathways more effectively than non-homologous end-joining, contributing to the higher biological effectiveness of high-LET radiation [59]. Leveraging these differences in DNA repair mechanisms can optimize cancer therapy and aid in developing targeted radiosensitizers.

X-Ray Irradiation

X-rays, a high-energy form of electromagnetic radiation, have revolutionized both medical and industrial applications due to their remarkable penetration capabilities (Figure 7) [60]. These waves, with wavelengths ranging from 10 pm to 10 nm and energies typically between 100 eV and 500 keV, possess unique properties that allow them to penetrate dense materials, enabling imaging and therapeutic interventions across a broad spectrum of fields (Figure 8) [61]. In the medical realm, X-rays are indispensable for diagnostics, including radiography and computed tomography (CT), and for therapeutic applications such as sterilization of single-use devices, where X-ray sterilization is emerging as an alternative to traditional gamma radiation [62].

X-ray imaging remains a cornerstone of clinical diagnostics, with techniques like radiography and CT relying on the differential absorption of X-rays by various tissues to produce high-resolution internal images. These modalities are critical for detecting cancers, bone fractures, and other medical conditions [63]. Recent advances include the development of dual-energy and multi-spectral CT, which enable quantitative tissue analysis and material characterization, offering improved diagnostic accuracy and interventional guidance [64]. However, the associated risks of radiation exposure necessitate strategies to minimize harm to both patients and medical staff.

The mechanism of X-ray generation, known as bremsstrahlung or “braking radiation”, occurs when high-energy electrons decelerate as they interact with atomic nuclei. This process produces a broad spectrum of X-ray energies, making it the cornerstone of X-ray production in medical and industrial settings [61, 65]. Recent advancements in bremsstrahlung include the development of electron wavefunction shaping techniques, which have demonstrated enhanced X-ray intensity and emission control when electrons interact periodically with crystalline materials [66]. Additionally, accurate modelling of bremsstrahlung production has refined predictions of X-ray energy and angular distributions, enhancing applications ranging from industrial inspection to advanced imaging techniques [67].

The biological effects of X-rays are primarily mediated through their interaction with DNA, leading to complex DNA damage (CDD), including double-strand breaks (DSBs) [68]. These lesions activate the DNA damage response (DDR), initiating pathways such as cell cycle arrest, DNA repair, and apoptosis [69]. Radiotherapy leverages this property to target cancer cells, exploiting their impaired repair mechanisms to induce cell death. Recent research highlights the potential of targeting DNA repair pathways to enhance radiosensitivity in tumors, thereby overcoming radioresistance while protecting normal tissue [70]. Emerging approaches, such as mitophagy enhancement, further illustrate innovative strategies

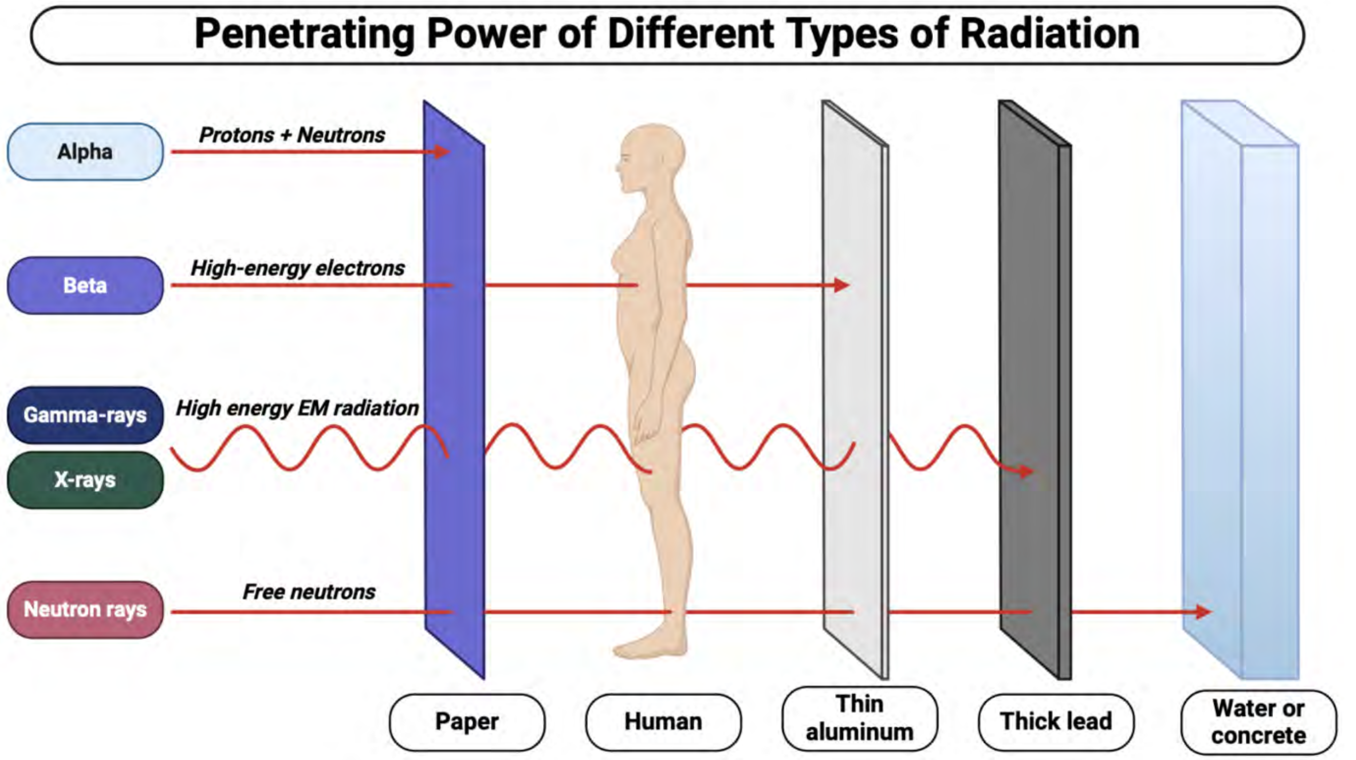

Fig. 7. Comparative penetrating power of various radiation types through different materials

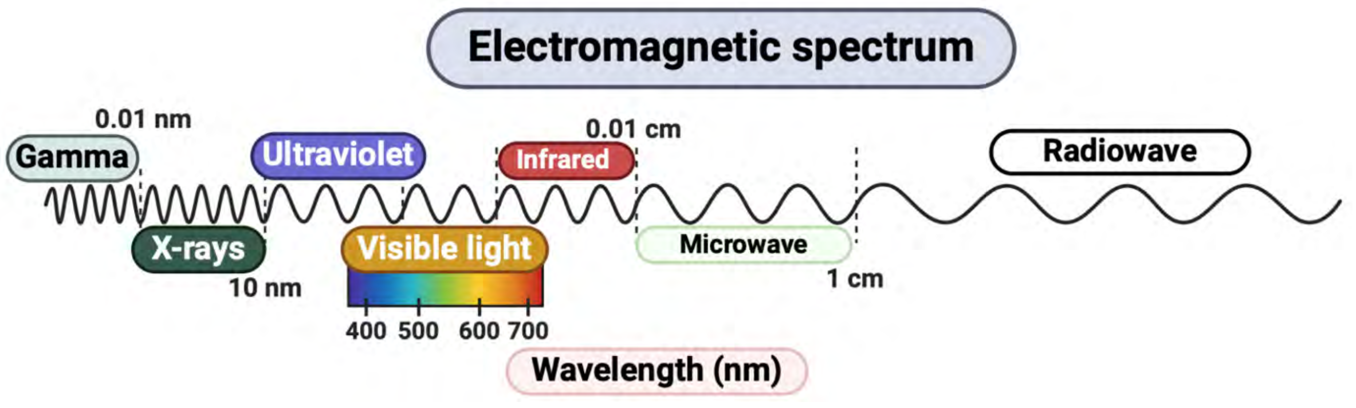

Fig. 8. Representation of the electromagnetic spectrum highlighting X-rays and other radiation types by wavelength range

to amplify radiation-induced DNA damage, paving the way for improved therapeutic outcomes [71].

X-rays also enable hybrid imaging techniques, such as X-ray-induced optical molecular sensing. These methods combine scintillation or Cherenkov radiation with molecular probes to achieve high-resolution imaging of tissue properties like oxygenation and pH, offering novel diagnostic opportunities [72]. Advances in scintillation materials, such as all-inorganic perovskite nanocrystals, have further improved X-ray detection efficiency, enhancing both medical and industrial imaging [62].

In industrial applications, X-rays are widely used for non-destructive testing and cargo screening. Dual-angle X-ray systems, such as those designed with 9 MV linear accelerators, have demonstrated improved contrast sensitivity and spatial resolution, ensuring precise inspections [73]. The development of wearable dosimeters for personnel protection, incorporating artificial intelligence and Internet of Things technologies, reflects the ongoing innovations aimed at optimizing X-ray safety in various fields.

Despite these advancements, challenges persist. Secondary radiation, such as that generated by bremsstrahlung, and the need for precise beam collimation complicate X-ray applications in both medical and industrial contexts [74]. Additionally, optimizing dose delivery while minimizing radiation-induced harm remains a critical area for research and development. As our understanding of X-ray interactions with biological tissues and materials deepens, future innovations will undoubtedly expand the potential of X-rays as a versatile tool for imaging, therapy, and diagnostics.

In-depth analysis of electron therapy in radiation treatment

To begin with, any therapeutic technique (whether established or emerging) must undergo rigorous evaluation from multiple perspectives, in context both its current advantages and inherent limitations. This approach is especially crucial in radiotherapy, where therapeutic decisions directly impact patient health and survival outcomes. Electron therapy, with its potential for high precision and adaptability, presents significant benefits across various clinical applications. However, a thorough understanding of its role demands not only an appreciation of its strengths but also a critical examination of its limitations and associated challenges. In this section, we aim to provide a comprehensive overview of electron therapy as an advancing modality. Through an analysis of current literature and recent innovations, we seek to offer a balanced perspective on its clinical promise, as well as the barriers that may influence its broader adoption in oncology.

Advantages of electron therapy in radiation oncology

Unique dosimetric properties of electron therapy

Electron therapy offers a distinct advantage in radiation oncology due to its unique dose distribution characteristics. Unlike traditional photon radiation, electron beams provide a homogeneous dose profile within the target area, with a sharp dose fall-off beyond a specific depth. This property makes them particularly effective for superficial tumors and cutaneous lymphomas, minimizing damage to underlying healthy tissues [75]. The steep dose gradients of electron beam also allow precise treatment of irregularly shaped targets while sparing adjacent organs and tissues [31]. Very High-Energy Electron (VHEE) beams, operating at energies above 100 MeV, have expanded the scope of electron therapy to include deep-seated tumors up to 15 cm depth. These beams offer improved dose conformity and reduced lateral scattering compared to photon beams, making them suitable for treating challenging anatomical regions [76].

Adaptability for Targeting Tumors at Various Depths

One of the most notable benefits of electron therapy is its adaptability. The ability to adjust beam energy allows for tailored treatments targeting tumors at varying depths. Low-energy beams are ideal for shallow lesions, while higher-energy beams address deeper tumors. For instance, electron therapy has shown efficacy in breast cancer treatments, particularly as a boost modality after breast-conserving surgery. Studies demonstrate reduced radiation doses to critical structures such as the heart and contralateral breast, maintaining high target coverage [77]. Recent advancements in hybrid techniques, such as combining electron and photon therapy, have further optimized treatment outcomes [17]. The use of 3D-printed modulated electron boluses (MEBs) has improved dose conformity and reduced exposure to organs at risk, including the ipsilateral lung and left anterior descending artery [78]. These innovations underline the potential of electron therapy to enhance patient quality of life.

Advancements in Very High-Energy Electron Therapy

VHEE therapy becomes a pioneering technique in modern radiotherapy due to its unique physical properties and potential to treat complex cancer cases [19]. Using electrons with energies in a wide range, it is characterised by its ability to deliver therapeutic doses with remarkable precision, which makes it particularly suitable for the treatment of tumours in heterogeneous and anatomically complex areas such as the thoracic and pelvic cavities (including the retroperitoneum and pelvic organs) [34].

Comparative analyses have demonstrated that VHEE beams achieve dosimetric performance similar to advanced modalities like proton therapy, offering an effective yet potentially more accessible alternative for institutions without proton beam facilities. Advanced beam delivery systems, including collimation and modulation techniques, have further enhanced this precision. Recent innovations in treatment planning, such as adaptive optimization algorithms, have enabled tailored dose distributions to accommodate tumors with irregular geometries or varying densities [79], underscoring the versatility of VHEE in clinical practice. As research progresses, the application of VHEE beams continues to evolve, with ongoing studies focusing on optimizing treatment protocols, refining beam delivery systems, and enhancing patient outcomes. By addressing existing technical challenges and expanding its clinical capabilities, VHEE therapy holds immense promise as a cornerstone of next-generation radiation oncology.

Innovative Delivery Systems and Emerging Technologies

Technological innovations continue to expand the versatility of electron therapy. *Laser Wakefield Acceleration* (LWFA) offers a compact and cost-effective method for generating high-energy electron beams, potentially making electron therapy more accessible in clinical settings [80]. Researchers have demonstrated the generation of ultrarelativistic electron beams up to 50 MeV using terawatt-scale lasers, paving the way for advanced radiotherapy devices [81]. Advanced collimation and scanning systems are also under development to support the precise delivery of VHEE beams. These systems incorporate optimized magnetic fields and high-Z foils to sustain ultra-high dose rates while ensuring dose uniformity. Combined with PBS techniques, these innovations enhance the precision and safety of electron therapy, reinforcing its role as a cornerstone in modern radiation oncology.

Biological Applications and Potential of Electrons

Electron therapy has emerged as a versatile modality in radiation oncology, offering unique biological and dosimetric advantages. Low-energy electrons (LEEs) play a crucial role in inducing DNA damage, primarily through ionization and excitation, leading to double-strand breaks (DSBs) and oxidative stress in tumor cells [82]. These effects are highly localized, minimizing collateral damage to healthy tissues. Advanced computational tools, such as Monte Carlo simulations, have provided insights into the interactions of LEEs with biological molecules, aiding in precise future treatment planning.

Recent innovations, such as *Very High-Energy Electrons* have expanded the potential of electron therapy to treat deep-seated tumors [32]. Studies demonstrate that VHEEs can achieve dosimetric quality comparable to proton therapy, particularly for challenging cancers such as glioblastoma and prostate cancer [57]. Furthermore, the integration of electron therapy with emerging modalities like FLASH radiotherapy has shown promise in enhancing the therapeutic index. VHEE beams are particularly suited for FLASH applications, offering both biological and ballistic advantages for treating deep-seated tumors.

Limitations and challenges of electron therapy

Despite its significant potential, electron therapy faces several limitations and challenges that restrict its broader clinical application. One of the primary limitations is the restricted penetration depth and dose modulation of conventional electron beams. Their shallow penetration depth makes them less effective for treating deep-seated tumors, even though there's a lot of research of this flaw. Thus, *Very High-Energy Electrons* partially address this limitation by providing improved dose matching for tumors located at a depth of 5–15 cm. However, achieving such precision requires energies above 100 MeV, for greater penetration depths — up to 30 or more centimeters deep, and advanced beam modulation techniques and highly specialized delivery systems. These setups, while promising, are not yet widely available and require further technological development.

Another critical issue is the presence of secondary radiation components, particularly *Bremsstrahlung* photons generated by high-energy electron beams. These secondary photons can contribute up to 8% of the absorbed dose [83], increasing the risk of unintended biological effects, particularly in high-energy applications. This underscores the importance of careful machine design and optimization of beam delivery systems to mitigate these risks. Accurate dosimetry and beam monitoring also present significant challenges, especially in ultra-high dose-rate applications such as FLASH therapy. Existing detectors struggle with saturation effects, limiting their ability to measure doses accurately at the speeds required for FLASH [84]. The development of robust monitoring tools and the standardization of dosimetry protocols are essential to ensure precise and safe dose delivery.

The scattering dynamics and lateral penumbra of electron beams further complicate their use, particularly in heterogeneous tissues. Advanced techniques such as pencil beam scanning (PBS) and magnetic focusing have demonstrated potential in reducing lateral penumbra and enhancing dose conformity [85]. However, these technologies are still in experimental stages and require further refinement to become clinically viable. In addition, the technical challenges associated with FLASH and VHEE therapy remain a significant bottleneck. Achieving the ultra-high dose rates necessary for FLASH therapy involves overcoming hurdles such as rapid energy adjustments and efficient pencil beam scanning for large treatment fields [84]. Current systems lack the capability to deliver FLASH dose rates across extensive areas, limiting their practical application. The development of advanced technologies is necessary to address these issues.

Finally, biological uncertainties surrounding electron therapy must be resolved. The relative biological effectiveness (RBE) of electrons, often assumed to be unity, may vary depending on factors such as energy levels, dose rates, and tissue types. While preliminary studies have reported differences in DNA double-strand break (DSB) induction between conventional and VHEE beams [86], the clinical significance of these findings remains unclear. A deeper understanding of the underlying radiobiological mechanisms is crucial to optimizing treatment outcomes and minimizing potential side effects.

Conclusion

Electron therapy represents a promising advancement in radiation oncology, offering unique physical and biological properties that enable precise and adaptable treatment strategies. Its dosimetric advantages, particularly the ability to deliver highly localized doses with minimal collateral damage, position it as a valuable modality for both superficial and deep-seated tumors. Recent innovations, such as *Very High-Energy Electrons* and FLASH radiotherapy, have expanded the scope of electron therapy, demonstrating significant potential for improving therapeutic outcomes and patient quality of life.

But several challenges remain. The limited availability of advanced delivery systems, complexities in beam modulation, and biological uncertainties, like variations in relative biological effectiveness, underscore the need for continued research and technological development. Addressing these limitations through interdisciplinary collaboration and innovation will be essential for unlocking the full potential of electron therapy as a standard clinical modality.

By bridging the gap between emerging technologies and clinical application, future efforts in electron therapy hold the promise of transforming radiotherapy practices, enhancing precision, and ultimately improving outcomes for cancer patients worldwide.

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Формирование будущего лучевой терапии: роль электронов и FLASH-подхода

М.А. Паршенков ✉, П.П. Сковородко, Д.А. Петрусевич, Ш.Н. Макаева, С.Г. Осипова, Г.Р. Ибрагимова, А.О. Истягина, К.А. Балаева, Г.М. Родионова

Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет),
г. Москва, Российская Федерация
✉ misjakj@gmail.com

Аннотация. Лучевая терапия (ЛТ) остается краеугольным камнем в онкологии, предоставляя целенаправленное лечение различных видов злокачественных новообразований (ЗНО). История ее развития уходит корнями к открытию рентгеновских лучей Вильгельмом Рентгеном и исследованиям радия Марии Кюри. Сегодня ЛТ превратилась в сложную область, охватывающую широкий спектр методов. Однако растущая глобальная проблема ЗНО различных органов подчеркивает необходимость постоянных инноваций для повышения эффективности лечения при минимизации побочных эффектов. Традиционные методы, такие как рентгеновские и гамма-лучи, доказали свою значимость в лечении различных видов рака, но тем не менее, часто сопровождаются непреднамеренным повреждением здоровых тканей. Электронная терапия становится перспективной альтернативой благодаря уникальным дозиметрическим характеристикам, обеспечивающим точное воздействие с ограниченной глубиной проникновения. Низкоэнергетические пучки электронов идеально подходят для лечения поверхностных опухолей, в то время как электроны очень высокой энергией (ЭОВЭ) позволяют воздействовать на глубокие опухоли, соперничая с протонной и тяжело-ионной терапиями. Кроме того, эффект FLASH — феномен, снижающий токсичность для здоровых тканей при сверхвысоких дозах, открывает новые возможности для улучшения качества жизни пациентов. Однако, несмотря на эти достижения в данной области, остаются многочисленные вопросы и вызовы. Ограниченная глубина проникновения, вторичное излучение от тормозного излучения и сложности в системах доставки доз ограничивают широкое клиническое применение. Кроме того, нерешенные биологические вопросы, такие как изменчивость относительной биологической эффективности, требуют дальнейших исследований. Настоящий обзор посвящен обсуждению уникальных преимуществ и ограничений электронной терапии в сравнении с традиционными методами. В нем рассматриваются новейшие достижения (ЭОВЭ, терапия FLASH и гибридные подходы), а также обсуждаются технологические вызовы и будущий потенциал электронных пучков в онкологии. Выводы. Интеграция с последними технологическими достижениями позволяет электронной терапии переосмыслить терапевтические подходы, предлагая более безопасные и персонализированные стратегии лечения злокачественных новообразований.

Ключевые слова: лучевая терапия, электроны очень высокой энергией, ускорители частиц, сверхвысокодозная терапия, онкология

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Corresponding author: Parshenkov Mikhail Alekseevich — junior researcher at the department of "Toxicological and Pharmaceutical Chemistry" of the Institute of Pharmacy of the First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Russian Federation, 119435, Moscow, Bolshaya Pirogovskaya St. 2, pp. 4. E-mail: misjakj@gmail.com
Parshenkov M.A. ORCID 0009-0004-7170-8783
Skovorodko P.P. ORCID 0009-0000-5624-4731
Petrusevich D.A. ORCID 0009-0005-2283-6372
Shagun N.M. ORCID 0009-0008-3396-6684
Osipova S.G. ORCID 0009-0006-6457-9543
Ibragimova G.R. ORCID 0009-0007-0478-7137
Istyagina A.O. ORCID 0009-0001-3295-8462
Balaeva K.A. ORCID 0009-0002-2930-6006
Rodionova G.M. ORCID 0000-0002-0536-9590

Ответственный за переписку: Паршенков Михаил Алексеевич — младший научный сотрудник кафедры токсикологической и фармацевтической химии им. А.П. Арзамасцева Института фармации им. А.П. Нелюбина Первого Московского государственного медицинского университета Министерства здравоохранения Российской Федерации (Сеченовский университет), Российская Федерация, 119435, г. Москва, ул. Большая Пироговская, д. 2, стр. 4, E-mail: misjakj@gmail.com
Паршенков М.А. SPIN 7012-6284, ORCID 0009-0004-7170-8783
Сковородко П.П. ORCID 0009-0000-5624-4731
Петрусевич Д.А. ORCID 0009-0005-2283-6372
Макаева Ш.Н. ORCID 0009-0008-3396-6684
Осипова С.Г. ORCID 0009-0006-6457-9543
Ибрагимова Г.Р. ORCID 0009-0007-0478-7137
Истягина А.О. ORCID 0009-0001-3295-8462
Балаева К.А. ORCID 0009-0002-2930-6006
Родионова Г.М. SPIN5657-9984, ORCID 0000-0002-0536-9590