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# Advancements in Radiotherapy: Precision Techniques for Enhanced Tumor Targeting

**Doaa mohammed hadi**
AL-Mustaqbal University, College of Science, Department of Medical Physics

**Ahmed Rabie Jaber Mustafa, Ali Karim Mohsen, Hussein Kadhim Abdel sada**
Department applied medical physics, Hilla University College

**Ali Mardan Katea**
Department applied medical physics Al_Hilla University College

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**Annotation:** Cancer incidence continues to surge globally, with an estimated 21.96 million cases and 10.05 million deaths in 2018. Cancer is currently the second leading cause of death and is responsible for an estimated 1 in 6 deaths worldwide. Oncology, through a combination of procedures such as surgery, chemotherapy, radiotherapy, immunotherapy, hormonal therapy, and more, provides treatment to patients diagnosed with malignancies. Radiotherapy as a treatment modality has become increasingly successful in recent decades. Radiotherapy alone or in combination with palliative or curative intent is commonly used in around 50 percent of cancer cases. Although numerous breakthroughs have improved patient outcomes worldwide, intense side effects are often associated with all common cancer treatments. Among the diverse treatment options available for cancer, radiotherapy stands out as an essential tool for both palliative and curative management. As part of a multidisciplinary approach to cancer management, the clinical practice of radiotherapy has evolved over the years. Until the last decade, cancer centers transformed from moderate-sized facilities focused on large fields and simple techniques to being megacenters at the

forefront of cutting-edge technology, which can deliver pinpoint treatments with sub-millimeter precision. The learning curve for radiation oncologists is steep, given the fact that cancer care is a large and rapidly expanding area requiring a strong knowledge of clinical oncology, radiation biology, medical physics, and radiobiology. Traditional radiotherapy techniques to advance tumor conformation and reduce the dose to normal tissue are also being replaced by different precise and targeted techniques.

### 1.1. Overview of Radiotherapy in Cancer Treatment

Radiotherapy uses high-energy irradiation to target cancerous cells and tissues, exerting its cytotoxic effect through a variety of cellular processes such as the obliteration of DNA repair. Radiation therapy has a long clinical history and can be applied across all stages of cancer management, including as an adjunctive therapy, with both neoadjuvant and adjuvant aims, preoperatively to reduce tumor size, and even postoperatively for eradication of residual disease. However, it is a commonly employed and effective therapeutic modality for clinical palliation, either aiming at the symptomatic approach by shrinking a certain tumor, mainly in head and neck cancers, in addition to those patients suffering from painful bone metastases, or those with end-stage or disseminated diseases. In addition to sole radiotherapy, it is quite frequently delivered either as a 'concurrent' adjuvant therapy alongside surgery, in the trimodal approach, or also combined with chemotherapy or other performance-modifying agents in order to enhance both local and systemic tumor control. [1][2][3]

The outcomes of radiotherapy in cancer care are heavily reliant upon an individual's unique bio-psycho-social profile, with inter- and intra-patient variations in terms of the enhancement in survival and/or quality of life being very disease-specific. Circumstances such as an advanced-stage disease at initial diagnosis would also significantly limit the curative nature of the radiotherapy, predominantly with a 5-year survival rate. In this regard, there is a growing need for developing enhanced, as well as rapid-acting, personalized care strategies; this would help to improve treatment responses, enhance functional outcomes, reduce the duration of overall therapy, and minimize the risk of side effects, thereby enhancing patient compliance. Over the multifactorial complexities within the cancer management and radiotherapy paradigms, personalized care often trails back to the biological factors underlying a patient's disease. In this way, the precision of cancer care can be significantly enhanced by tailoring planning and delivery-related techniques. By doing so, one can facilitate the optimization of the synergy between multiple modalities for treating any particular stage of the cancer. [4][5]

### 1.2. Importance of Precision Techniques

The rapid evolution and advancements in radiotherapy technology have made it possible to precisely target tumors far better than in the past. The clinical importance of these developments and the benefits from the use of more targeted, higher-dose radiotherapy have been shown to be substantial in terms of tumor control, reduction in side effects, and overall survival in many clinical trials. In general, these improvements have occurred because radiation therapy can now be delivered more precisely to the intended tumor target, thereby reducing the dose to surrounding organs and normal tissues. For this approach to be successful, the treatment must be very carefully planned and must be delivered with a high level of precision that is certain to be achieved consistently during treatment.

Information and communication technology has helped realize radiotherapy techniques with high precision in both treatment planning and delivery, such as 3D isolated fields, IMRT, VMAT, IGRT, and adaptive strategies. This increased precision is especially important for complex or locally advanced tumors located near dose-limiting normal organs and structures, such as head and neck tumors, lung tumors, gynecologic tumors, brain tumors, liver tumors, and tumors of the digestive system. Such tumors are often situated in highly intricate and secretive harmony with the surrounding anatomy—joint, fascial sheaths, and glands. Recently, great advances in tumor biology have been recognized, and it is now known that each tumor is an individual entity with different histological, biological, physiological, and radiological characteristics. Thus, it is very important to understand the concept of tumor biology and to tailor the treatment according to the field of the individual. The tailoring of treatment in radiotherapy advances in such a way that the target volume is individual, which is characteristic of precision strategies. [6][7][8]

## 2. Fundamentals of Radiotherapy

Radiotherapy involves the targeted delivery of ionizing radiation to kill or control the growth of malignant tumors by acting on their cellular organelles and genetic material. The physics of radiation oncology is such that the intensity of the tissue dose is highest at the treatment site and decreases gradually in the surrounding normal tissues for a desired radial and longitudinal extent. Electromagnetic and particulate radiations are common types; they are known to cause significant cellular and subcellular biological damage.

At the cellular level, radiotherapy adversely affects the growth and reproductive potential of tumor and healthy cells to various extents. If a side effect is connected to the exponential effect, then the number of affected cells increases or decreases by a constant fraction per Gray. The goal of radiation therapy is to deliver the maximal tolerated tumor dose in the least time possible, maintaining normal tissue damage at a minimum. As the tumor doubles every 30 days, conventional radiotherapy takes between 35 and 40 days. In general, radiotherapies can be divided into two principal subtypes: external beam radiotherapy and internal radiation. The mode of radiotherapy selected is mainly based on the primary characteristics of the tumor and host.

While medical physicists create the equipment that delivers the radiation to the cancer sites, they ensure its delivery, safety, regulation, regulatory adherence, and documentation. Additionally, they assist in the development of new therapies such as particle therapy and stereotactic radiosurgery. It is essential that other medical colleagues participate in tumor board discussions, resulting in a consensus about the best way to treat the oncologic problem. This is where radiation oncologists come in to apply radiotherapy. [9][10][11]

### 2.1. Radiation Physics and Biology

The principles of physics and biology constitute the foundation on which radiotherapy is based. Radiation physics describes the interaction of photons, protons, neutrons, heavy charged particles, or electron beams with various materials, including the tissues of the human body. It elaborates on the principles of dosimetry and treatment delivery techniques while biology interfaces with our understanding of the biological effects of these radiations. Radiation biology describes how these radiations interact with biological tissues, the cellular response mechanisms to radiation, and the repair processes at the tissue level. Some of the cell populations essential for the assessment of radiation effects are found in the human body, which serve as biological dosimeters of radiation.

A very simplified principle might be that more radiation—of sufficient energy—aimed at a differential between levels of normal tissue tolerance and levels of tumor cell kill with acceptable consequences for the normal tissues would be expected to improve the attained local control and potentially survival rates until adequate levels of total tumor cell kill are reached. The fundamentals of the therapeutic ratio or window treatment are hypothesized on the basis that normal tissues exhibit a much greater capacity for repair and have a higher proliferation rate than the malignant or slowly proliferating cells found in tumors. A convenient classification of the basic physical factors relating to radiotherapy delivery may be used to provide a structure for understanding these issues. It has been modified in coherence with advancements and sophistication in technology. [12][13]

### 2.2. Types of Radiotherapy: External Beam vs. Internal Radiation

Radiotherapy comprises the treatment of cancers using various types of penetrating radiation. It is a local treatment administered to kill cancer cells in the body. Currently, the primary modes of radiotherapy include modalities of external beam treatment and internal radiation therapy. External beam radiotherapy involves exposing patients to high-energy beams directed at the cancer tissues. In internal radiation therapy, radioactive sources are placed temporarily within or just near a tumor, thus circling the therapy.

Electrically charged particles and X-ray photons are the primary high-energy sources from which radiotherapists currently treat with external beam radiation; all of the above can annihilate electrons to deposit lethal doses of energy within tumor target regions. Relevant external techniques include 3D conformal RT, intensity-modulated RT, gating and synchrony, and stereotactic body RT. Ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography, and X-ray imaging are all central to treatment planning purposes for both external and internal therapies. Radiation treatment of patients may utilize either of the two radiotherapeutic modes, external or internal sources, or both, depending on the specific character and location of cancer, the prospective clinical objectives, and concomitant patient dependencies. The techniques for escalated radiation doses have evolved over time in response to increasing needs from the clinic. The treatment techniques have tended to evolve from external means to internally directed treatments determined by the anticipated responses in healthy tissue. [14][15][16]

## 3. Evolution of Precision Techniques

The first use of ionizing radiation to treat cancer can be traced back to the end of the 19th century. External beam radiation therapy (EBRT) treats the tumor from outside the body by passing the ionizing radiation through the skin and the tissue. Since the early days of radiotherapy, it was recognized that these X-rays and gamma rays not only affected the tumor but also the surrounding healthy tissues. With these limitations, investigators started to develop techniques with the intent of delivering high radiation doses precisely to the tumor while minimizing the dose to the surrounding tissue. This led to the development of what is now known as precision techniques.

The first precision technique was image-guided radiotherapy (IGRT), which uses imaging studies conducted prior to and during radiation therapy to ensure the precise setup and positioning of the patient and to localize the position of the target tumor. A major advantage of IGRT is the ability to monitor and adjust for target and motion changes on a real-time basis during treatment. A further development is intensity modulation of the radiation beam. The delivery of radiation with varying intensities was shown to further enhance the local tumor control while minimizing the normal tissue effects. Intensity-modulated radiation therapy (IMRT), which uses multiple beam position techniques, treatment planning, and inverse treatment planning algorithms to deliver intensity-modulated radiation over the tumor. Another technique under the precision radiation oncology umbrella is stereotactic body radiotherapy (SBRT), which uses tight image and mesh immobilization and real-time tumor tracking. SBRT, also called stereotactic ablative radiotherapy, delivers high-dose radiation in small, high-dose fractions, safely and accurately to small tumors either inside or outside the brain. Furthermore, proton therapy will likely have an increasing role in the treatment of malignancy and will continue to receive attention from radiation oncologists and other investigators because of its advantages in sparing healthy tissues when compared to conventional photon therapy and because of its potential as a novel local therapy and radiosensitizer. [17][18]

### 3.1. Image-Guided Radiotherapy (IGRT)

3.1. Image-Guided Radiotherapy (IGRT) One of the most significant and consequential advances in radiotherapy treatment technology has been the creation of IGRT in the quest to improve the pinpoint accuracy and precision of radiotherapy treatment to the greatest extent possible. The essential idea is to generate sophisticated images showing the position of tumors and their relationship within the patients' normal tissues and then use the images to confirm that the patient is in the right position to deliver their treatment. The aim for IGRT is to ensure that the treatment is delivered to the tumor with a great degree of accuracy each and every time the patient receives treatment, allowing for tumor control as well with limited normal tissue injury. The purpose of IGRT is to observe and assess tumor position, the surrounding affected cells, and the possibility of the natural shifting or moving of these relative positions. To achieve this, a variety of imaging methods and processes can be used, such as computed tomography, magnetic resonance imaging, or ultrasound. These imaging techniques can be utilized individually or combined in one of a variety of ways, and the system can even be set up so that images can be taken directly in the treatment position. Another development in technology uses a linear accelerator to perform a real-time imaging process so that the tumor can be made visible while at the same time being treated. Advantages of this method are that both geometrical changes resulting from the position of the patient can be taken into account. Thus, this treatment is fully customized with significant management impact on patient management and patient survival. Early clinical studies comparing IGRT treatments to treatment plans based on less frequent pre-treatment imaging have demonstrated clear superiority in favor of IGRT studies, which have translated into excellent treatment results. In addition to normal radiotherapy treatment, image-guided treatment delivery is a new component for the use of nuclear medicine isotopes for treatment, minimizing residual disease or by reducing margins used for normal treatment medication, and recreating strict treatment plans for patient radiation. Both components require specific equipment and some technical skill in order to operate them properly. This procedure is too simple compared to traditional X-ray and teletherapy. The first advantage is the safe and fast setup of the system. Further, therapeutic processes would allow for greater freedom of movement and bedside-based handling by highly experienced staff. However, it should be mentioned that the economic and expenditure aspects are too high, for which the appropriate equipment system or operation may begin after a technologist or on-the-job training courses are instituted. [19][20]

### 3.2. Intensity-Modulated Radiation Therapy (IMRT)

### Intensity-Modulated Radiation Therapy (IMRT)

IMRT is an important landmark in the advanced techniques of radiotherapy. Technically, IMRT allows clinicians to vary radiation intensity or energy per beam by using multi-leaf collimators, making it possible to deliver a highly conformal radiation dose to the tumor while sparing the adjacent healthy tissues. There are different algorithms that are used for calculating dose distribution in IMRT treatments, and the sophistication of such algorithms results in sophisticated treatment planning systems for IMRT. All IMRT treatment planning systems follow a four-step procedure starting from the definition of at least one gross target volume and one target volume. Then, the relevant structures for dose specification are contoured, followed by optimization, and finally, dose evaluation and analysis are performed. IMRT, as compared to 3D-CRT, has been tested in several clinical studies and for different kinds of cancers, resulting in not only significant reduction in toxicities associated with adjacent organs at risk but ultimately leading to much better treatment outcomes. It is, however, worth mentioning that IMRT planning is complex, time-consuming, and requires advanced computing and treatment delivery systems.

IMRT has been shown to improve the quality of life of the patients as well as to improve tumor control rates for a number of different sites. For example, it was reported that head and neck cancer patients treated with IMRT were free of disease for over 70 months following treatment. A similarly high five-year local control rate and overall survival were also reported for prostate cancer patients who were treated with IMRT. Additionally, combined doses of stereotactic IMRT and chemotherapy showed good results for inoperable lung cancer patients. These are a few selected examples that truly represent an individual patient's good prognosis. The significant impact of IMRT on improving patients' prognoses is also evident from several other studies integrating innovative IMRT treatment planning and sophisticated computer models. This progress has accelerated the launch of national multidisciplinary centers dedicated to patient care and quality assurance. All the above-mentioned advantages have not only encouraged modern radiotherapy but have also resulted in several forms of IMRT. In the next section, we review the study for early-stage larynx cancer. [21][22]

### 3.3. Stereotactic Body Radiotherapy (SBRT)

Stereotactic Body Radiotherapy (SBRT) Stereotactic radiotherapy (SBRT) has, in the last few decades, emerged as a cutting-edge technique capable of targeting tumors with increased precision. Stereotactic radiotherapy systems use advanced imaging systems to locate and precisely position tumors in order to deliver high-intensity doses of radiation in a lesser number of sessions than conventional radiotherapy. The main advantage of SBRT is that it allows significantly increased precision of tumor targeting. As a result, this treatment may be useful for patients with inoperable tumors or tumors in difficult anatomical locations, thus often offering a better prognosis. Clinical results for SBRT have demonstrated very promising tumor control and very low side effects, with curative outcomes in many patients with organ-confined tumors, such as lung and prostate cancer. In normal procedure terms, SBRT can be seen as a seamless evolution of modern radiotherapy practice. However, from a technical planning view, this evolution represents a number of formidable challenges. Chief among these is that moving all the degrees of freedom to the planning phase has a major impact on treatment quality and planning uncertainty. The planning of such treatments requires a robust optimization of a large number of highly dynamic delivery parameters that vary significantly as a function of time. For a good outcome, the selection of patients for SBRT needs to be guided by clinical indications. International experience in the planning, delivery, and clinical outcomes of SBRT allows for an increasing amount of guidelines for everyday clinical use, and several trials are investigating long-term outcomes and improvements of SBRT treatment. [23][24]

### 3.4. Proton Therapy

Due to being designed based on the fundamental principle of 'Bragg peak,' proton therapy is unique compared to photon-based therapies. Charged protons have different interactions with tissues as opposed to photons, especially low-end protons that deposit less energy and exhibit charge and mass dependence on biodistribution, which results in a gradient of lateral and distal dose fall-off around the target volume. Usually, around a centimeter before the end of the range, there is a sharp increase in dose deposition allowing for energy withdrawal. The rest of the energy is steeply distributed along the entrance channel, which causes minimal exit dose. Hence, negligible dosages are absorbed by distant tissues post-proton 'Bragg peak.' Proton therapy, one of the most advanced modalities in the arena of highly advanced precision radiotherapy, is externally administered to tumors effectively for radiotherapy. The clinical acceptability of the utilization of proton beams was seen within the management of intracranial, head and neck, liver cancers, pediatric and adult cases, as well as other medical indications. It should similarly be noted that, predominant to date, pediatric tumors have shown a beneficial response to lower administered radiation dosages. Central lung cancers, parameningeal sarcomas, and near-critical sites such as the spinal cord, vesicular organs, and paraspinal sites stand to benefit from proton beam treatment, which avoids exposing the quantity of tissues near the tumor to harmful doses of radiation. It is also relevant to note that these tumors are often close to the midline of the body and tend to move during respiration. Hypothetically, since protons follow the movement of the adjacent light tissues, these tumors could safely be exposed to large doses of radiation while minimizing the dosage to the healthy tissues of the lightweight visceral organs. Additionally, compared to standard treatment modalities, proton therapy accounts for reducing side effects and imparting an overall enhanced quality of life. Primarily, the main advantage of this therapy is its ability to enhance the management of tumors in terms of imposing control on primary and metastatic sites by executing its numerous technical capabilities in clinical scenarios, particularly against penetrating and radiobiologically important types of tumors. Lastly, the aim is to encompass other factors in the manuscript, such as the challenges to proton therapy. These factors undermine protons' advantage by unjustifiably escalating the aforementioned. [25][10]

## 4. Role of Imaging in Precision Radiotherapy

Imaging plays a critical role in the development and successful operation of precision radiotherapy. It supports the entire process, including the location of treatment areas, the specific execution of treatments, and patient response. Imaging is utilized in planning, simulation, adaptation, and verification, providing valuable data at various scales. At a diagnostic level, computed tomography and magnetic resonance imaging facilitate base-of-skull and iso-dose surface comparisons post-cranial irradiation. Combined or alternative positron emission tomography and computed tomography offer multi-modal imaging for tumor histology visualization and functional tumor response evaluation. In addition to fluoro-deoxy glucose, other PET tracers, such as fluoroethyltyrosine, carbon-11-L-methionine, and other novel, specific, radioactive fluorine tracers are available. These scans have overcome radiological chondrosarcoma and neurofibromatosis diagnostic limitations involving high rates of false-negative diagnosis, differentiating radiation necrosis from tumor progression, and facilitating radiotherapy treatment planning.

In radiotherapy planning and execution, treatment imaging offers verification and adaptation of target structures and their interfacing regions based on continuous patient and tumor position or volumetric changes. Furthermore, radiotherapy workflows apply advanced imaging modalities for real-time treatment imaging delivery for cone-beam and mega-voltage imaging prior to radiation beam exposure. Veterinary case studies have provided evidence for improved radiation therapy outcomes for modalities that ensure accurate pre-radiation imaging at the time of therapeutic radiation delivery. Development in the design and integration of tomographic planning simulation and treatment imaging systems has thus influenced the safe and powerful treatment delivery that modern radiotherapy systems ensure.

Imaging has become an essential part of precision radiotherapy, having significantly improved our capacity to identify and localize many tumors and some benign lesions. Combined with major advances in imaging, treatment delivery systems in radiotherapy have also evolved significantly to improve precision. Periodically, early experiences with existing approaches to multi-modality treatments may show little toxicity; this may be attributed to the two elements operating together. In this setting, the effectiveness of each part of the treatment cannot be separated, forming a holistic rather than an additive package of care. It is likely that prospective clinical trials of treatment delivery as technology evolves further toward interventional techniques would show a different pattern of toxicity. With advancements in target localization and dose delivery, the nature of the imaging needed in radiotherapy is increasingly moving toward image-guided radiotherapy. However, the increased volume and complexity of modern radiotherapy are likely to be both reflected in and driven by computed tomography, with the principles of linear energy transfer and relative biological effectiveness becoming less relevant. Long before modern treatment delivery, the basis of the prescription lies in the principles of physical dose in gray relating to effective acute toxicity as predicted by linear energy transfer and therefore prescribed to the edge of the target. Image guidance has become an essential part of the safety of radiotherapy. Application of contemporary CT imaging techniques helps qualify the total body volume being treated with or without an irradiated organ of parallel function, which helps to predict potential common acute morbidity like fatigue, weight loss, taste change, nausea, and diarrhea. With respect to brachytherapy, the ability of intracavitary MRI is a significant step forward in soft tissue delineation for image-guided brachytherapy. [26][27]

## 5. Advantages and Challenges of Precision Techniques

Precision techniques in radiotherapy are considered to be the cutting edge of the development of treatment delivery systems for cancer. The accruing wealth of imaging and radiotherapy data, including genotypic and radiomic findings, screens both patients and their tumors, cell by cell for a cumulative character allowing a treatment plan and a delivery system to be built to optimally fit the characteristics of a particular cancer and patient, and to cater for individual intra-fraction patient motion allowing dose delivery directly to the tumor cells. Furthermore, by increasing the dose delivered to tumor targets while controlling doses to the immediately surrounding tissue, the missing link in advancing radiotherapy from being endurable to being a curative tool is potentially possible. Indeed, evidence suggests an increased therapeutic benefit to patients with a decreased likelihood of side effects and toxicity, allowing clinicians to tailor treatment delivery to the requirements of each individual patient and respective tumor. As with any progression, there are natural challenges that are currently being faced, such as the technological and infrastructural demands to deliver such therapies, ethical considerations for the nature of healthcare delivery and access, and the potential cost burden for the implementation of such campaigns. Although there have been great leaps in technology, there is still much that we do not yet understand and subsequently need to design around to ensure that the greatest patient benefit can be optimally provided. As such, training of healthcare professionals continues to be the hallmark of progress, to ensure that we move with the times and maintain our ability to deliver appropriate care to our patients using these state-of-the-art tools. The level of complexity associated with implementing such systems cannot only be described and captured or developed by abstract technical developments, yet they are also a reflection of the challenges faced when being embedded into clinical management. A couple of case studies will be explored to provide further understanding of these questions. [28][29][30]

## 6. Clinical Applications and Case Studies

Precision radiotherapy is an increasingly important weapon in the radiotherapy armamentarium across a variety of histologies. This section contains a series of clinical case examples that bring together written and visual information on the use of some of these techniques in routine practice. These case studies illustrate the potential value of some newer techniques and the close involvement of a multidisciplinary team managing advanced and complex patients; they include some of the clinical challenges and solutions that radiotherapy can address, many maximizing the differential between tumor and normal tissue target volumes. These examples provide information on the clinical indications and pathways, planning and treatment parameters, clinical outcomes and follow-up, and how these precision techniques are integrated within real-world patient scenarios. Statistical analysis with follow-up of over 5 years indicates superior long-term outcomes for those treated using figure of 8 stereotactic body radiotherapy, with local progression-free survival 60-70%. CT-based planning showed that including a 5mm target volume ensured a truly free margin from potential geographical misses of approximately 99.9%. A total of 270 liver metastases from 9 histological subgroups were treated with 4 Gy x 10 fractions. Actuarial overall survival, local progression-free survival, and distant metastasis-free survival at 10 years were 25%, 52%, and 30% respectively. Patient status post-selective internal radiation therapy was a significant factor for overall survival. In the series of 181 pulmonary oligometastases, with available volumetric data, after local therapy, only volumetric dose coverage as a continuous variable was significantly associated with local progression-free survival. Management of the primary tumor present at the time of oligometastases was not significantly associated with overall or local control, disease-free or overall survival. At the time of analysis, the 3-year local progression-free survival and overall survival following definitive local ablative treatment of the oligometastatic lesions were 93% and 84% respectively. The above findings show enhanced tumor targeting with a fall in marginal failures as an early manifestation of these techniques. More will become clear with longer follow-up in a considerable number of cases. [31][32]

## 7. Future Directions in Radiotherapy Research

Emerging technologies and novel radiotherapy strategies will have to be further explored in future directions for research in radiation oncology. Refining the precision in tumor targeting is one of the main directions of radiotherapy research. More advanced radiotherapy devices with increasingly sophisticated delivery capabilities will be introduced for clinical use in the near future. Research is needed to investigate the potential of these modalities for specific indications, and often the use of modern delivery systems requires a different and novel approach to treatment plan optimization. Integration of artificial intelligence and machine learning could be used to optimize treatment plans but can also be potentially used for modeling and predicting patient tumor responses. As the next level of combination therapy, the possibility of integrating other systemic therapies with radiotherapy could be considered. These potential collaborations fit within a broader initiative that is underway to start to envision what radiotherapy will look like at the larger research center scale. Principles that are being adopted and adapted by a number of groups are to adopt solutions rather than platform-based research strategies. This means that rather than starting with considering a specific treatment planning, delivery, or other technology, we begin by thinking about the clinical or cancer biology problem and allowing technology to emerge from the solution. When it comes to emerging technologies, there is a widespread recognition that it is critical to have solid preclinical data before technologies are translated to the clinic. It is therefore likely that research in the area of biology and physics will work much more closely together than they did in the past. We would also expect that there will be growing suggestions for more translational research such that hypotheses rooted in clinical biology will be tentatively tested in preclinical systems in order to underpin the rationale for clinical studies with early realization and inform trial design. This reflects a research environment where physics researchers have become increasingly dependent on clinician-driven research questions to drive their work. Finally, there has been a call internationally for the importance of basic research in all areas of radiation biology, physics, and clinical oncology. This we also include in our vision. The field of radiation oncology is in the process of transforming over the next years. These insights bring into focus optimistic hopes of progress but also stark realization of the work that remains to be done; it also highlights the importance of conversations with all key stakeholders in the community: researchers in the laboratory, conferencing center, and clinics; treating clinicians and other health professionals, physicists, engineers, and industry; and critically, our patients. This is a time of transformation in the history of radiation therapy and represents an exciting opportunity to bring researchers, clinicians, industry, and especially, patients together to explore the most promising opportunities for the next era of practice and investigation.

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