Recent Developments in Radiotherapy

Deborah E. Citrin, M.D.

It is estimated that 470,000 patients receive radiotherapy each year in the United States. As many as half of patients with cancer will receive radiotherapy. Improvements in diagnosis, therapy, and supportive care have led to increasing numbers of cancer survivors. In response, the emphasis of radiation oncology has expanded beyond cure to include reducing side effects, particularly late effects, which may substantially affect a patient’s quality of life. Radiotherapy is used to treat benign and malignant diseases and can be used alone or in combination with chemotherapy, surgery, or both. For primary tumors or metastatic deposits, palliative radiotherapy is often used to reduce pain or mass effect (due to spinal cord compression, brain metastases, or airway obstruction). Therapeutic radiation can be delivered from outside the patient, known as external-beam radiation therapy, or EBRT (see the Glossary in the Supplementary Appendix, available with the full text of this article at NEJM.org), by implanting radioactive sources in cavities or tissues (brachytherapy), or through systemic administration of radiopharmaceutical agents. Multiple technological and biologic advances have fundamentally altered the field of radiation oncology since it was last reviewed in the Journal.

Recent Technological Advances

Target Delineation

Defining the extent of a tumor, known as target delineation, is a critical first step in planning radiation treatments, since accurate localization reduces the chance of unintentional exclusion of tumor from radiation exposure and allows maximal sparing of normal tissues. Typically, radiation treatment planning begins with a simulation, in which a set of computed tomographic (CT) images is obtained while the patient is immobilized in a position deemed adequate for the radiation treatment. Complementary imaging studies, such as magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET), can be electronically fused to the planning CT scan or can be used as the primary imaging study for planning. In this way, complementary imaging techniques can be incorporated into the treatment-planning process. A margin of uninvolved, normal tissue adjacent to the tumor is often included in target delineation to account for variations in daily patient setup and alignment, motion of organs during treatment, and any uncertainty about the extent of the disease.

CT-based delineation of the radiation target is a great improvement over target delineation in the pre-CT era; however, CT still provides challenges for radiation oncologists. For example, lung cancers may cause airway obstruction and distal atelectasis, making it difficult to differentiate tumor from collapsed lung on CT images (Fig. 1). With the use of FDG-PET in patients with lung cancer, target volumes can be defined on the basis of metabolic activity, which correlates...
closely with pathological findings. As data have emerged that indicate that targeting only visible mediastinal tumor results in few isolated recurrences in lymph nodes that were not intentionally targeted, FDG-PET has had an increasingly important role in defining the extent of mediastinal disease and reducing the radiation volume in patients with lung cancer. Similarly, FDG-PET has contributed to delineation of the radiation target volume for a range of other tumor types, such as cervical cancer, lymphoma, and head and neck cancers.

For several cancers, such as central nervous system tumors, head and neck cancers, sarcomas, and cervical cancers, MRI, as compared with CT, provides enhanced visualization of the tumor and surrounding organs that are at risk for injury. MRI is susceptible to geometric distortion and artifacts, so consideration of these limitations and careful quality assurance procedures are key to its use for treatment planning.

As these advanced imaging techniques have improved the visualization of tumors, there is growing interest in highly conformal and focal radiotherapy, in which the radiation dose drops off rapidly outside the target.

TREATMENT PLANNING AND DELIVERY
The ability to more accurately define tumor targets has provided a strong rationale for devising radiation treatments that closely conform to the tumor, spurring refinements in radiation treatment planning, daily localization, and treatment delivery. Traditional radiation treatments deliver a consistent intensity of radiation across the treatment field. The development of dynamic multileaf collimators — small movable metal leaves that shape the radiation field and alter the intensity of radiation delivered to portions of the field and that are used in combination with confor-
mal radiotherapy — has exponentially increased the potential complexity of treatment plans. Defining how to alter the intensity of the beam to make the treatment most conformal requires advanced computation. This includes inverse treatment planning, in which dose goals and the relative importance of each goal are defined by the prescribing physician, and the treatment-planning system iteratively becomes better until an acceptable plan is generated. The delivery of modulated radiation beams, a technique known as intensity-modulated radiation therapy (IMRT), has resulted in the capacity to shape the high-dose region to match complex target volumes while maximally sparing surrounding normal tissues in a way that would not be possible with conventional radiation treatment methods. Additional refinements, such as volumetric-modulated arc therapy (VMAT), in which modulated treatments are delivered as the radiation treatment machine rotates in an arc around the patient, have both improved conformality (the ability to sculpt, or conform, the dose closely to the target) and reduced treatment times (Fig. 2).

Traditionally, patients were aligned for daily radiation treatment with the use of external skin marks and tattoos, and positioning was verified on the basis of weekly radiographs that correlated bony anatomy to treatment-planning images. The adoption of more conformal approaches has necessitated enhanced confidence in tumor location. Today, many linear accelerators are capable of performing CT imaging or high-quality digital radiography to ensure that the tumor is in the expected location. The use of frequent pretreatment imaging that references the original radiation plan, known as image-guided radiation therapy (IGRT), has increased certainty regarding tumor location for daily treatments. In some cases, small markers visible on radiographs, known as fiducial markers, can be implanted within or near the tumor for imaging before or during the treatment to ensure accurate localization.

Although patients can be immobilized reproducibly for daily treatment, tumors are often situated in organs that move with normal bodily functions: breathing, peristalsis, swallowing, filling, and emptying. A variety of approaches have been used to account for tumor motion. For example, patients can be asked to hold their breath during inhalation or exhalation for the planning

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**Figure 2. Comparison of Three-Dimensional Conformal Treatment Planning and Volumetric-Modulated Arc Therapy (VMAT).**

The pelvic lymph nodes (green) are the radiation target in this comparison of three-dimensional conformal treatment planning (Panel A) and VMAT planning (Panel B) in the same patient. The radiation dose to be delivered is indicated by lines that encompass that dose, known as isodose lines. The region receiving the prescribed dose is encompassed by the red line (100% dose line). In the VMAT plan, the prescribed dose tightly conforms to the intended target, and the dose to the rectum, bladder, and nontarget tissues of the pelvis is minimized. The arrows in Panel A represent the direction of the treatment beams. In the VMAT plan, treatment is delivered continuously as the machine completes an arc around the patient, indicated by the circle in Panel B.
scan and treatment. A recent advance is four-dimensional CT, which can be used to acquire treatment-planning images at multiple phases of the ventilatory cycle. This method provides an understanding of tumor motion during the ventilatory cycle, allowing the margin of normal tissue to be expanded in each direction only as much as needed to encompass the tumor during ventilation. Alternatively, treatment delivery can be restricted to phases of the ventilatory cycle in which the tumor falls within a prespecified location, a technique known as respiratory gating. Collectively, these methods serve to increase certainty about tumor location while minimizing unnecessary radiation to surrounding normal tissues.

Traditionally, radiation treatments have been fractionated, or broken into multiple doses, to leverage differences in radiation response between tumor and normal tissue, such as reoxygenation of tumor, repair, redistribution of tumor cells into sensitive phases of the cell cycle, and repopulation between doses. Fractionation of the total radiation dose can yield cures while reducing toxicity, as compared with single doses that are associated with similar tumor-control rates. In recent years, there has been substantial interest in regimens involving a relatively large dose per fraction and highly conformal techniques. With these regimens, ablative doses are delivered over a period of 1 to 2 weeks, in contrast to the previous standard of using protracted fractionation, with daily treatments lasting for many weeks. These highly conformal techniques, known as stereotactic body radiation therapy (SBRT) (also called stereotactic ablative radiotherapy [SABR]), have been used for both curative and palliative treatment and have demonstrated efficacy in randomized trials for some tumors.

The biologic rationale for SBRT is complex but presumes that the observed antitumor effect is a consequence not only of direct tumor-cell killing but also of indirect killing through mechanisms such as vascular collapse and immune effects. Since the doses delivered with SBRT are ablative, the therapeutic advantage of this technique can be realized only when the treatments are highly conformal to allow maximum exclusion of normal tissues. Thus, SBRT requires careful and reproducible immobilization of the patient, with organ motion accounted for and minimized and with a clear understanding of the extent of the tumor. SBRT is not appropriate if there is uncertainty about the extent of the tumor or if large volumes of normal tissue would require treatment to address the possibility of microscopic disease.

Stereotactic radiation treatment with the use of single doses or only a few fractions has been used for some central nervous system tumors for many years; however, expanding the treatment to extracranial tumors has been a more recent development. Emerging evidence suggests that SBRT can provide exceptional local control for a variety of tumor types and locations. Because patients are carefully immobilized and targeting is so precise, the treatment can be delivered with inclusion of only the smallest margin of surrounding normal tissue. Since the approach uses multiple-beam techniques or arc therapy (IMRT or VMAT), the dose drops off rapidly outside the target, minimizing the exposure of normal surrounding tissues to radiation doses exceeding their tolerance. Although SBRT approaches have been incorporated into clinical practice, they are not appropriate for all clinical scenarios, and the long-term toxicity and efficacy of these approaches are still being determined for many tumors and locations. The size of the lesion requiring treatment and its proximity to critical normal tissues with high sensitivity to radiation must be carefully considered.

Another method of delivering highly conformal therapy is the use of protons and heavy ions, which differ from the more commonly used electrons and photons in terms of how they interact with tissue and deposit the radiation dose, generally resulting in a reduced dose beyond the target (Fig. S1 in the Supplementary Appendix). Heavy ions, such as carbon ions, have shown promise in early clinical trials. Because of its tremendous cost, however, this technology is currently available at only a few centers around the world. In contrast, proton therapy is currently available at several centers in the United States. The benefit of proton therapy for many tumor sites, such as the prostate, remains unproved, given the paucity of evidence of greater tumor control or less toxicity with proton therapy than with other approaches. Many in the oncologic community are eagerly awaiting data from ran-
domized trials comparing current radiotherapeutic techniques with proton therapy. The use of protons is an accepted alternative with potential advantages over photon therapy for selected tumors of the central nervous system and for selected tumors in children.17,18

Brachytherapy, the implantation of radioactive sources in a body cavity or tumor, is perhaps the most conformal type of radiation treatment. This approach often allows delivery of higher doses than those delivered with the use of EBRT, since the radiation generally does not reach uninvolved normal tissue. For some tumors, the benefit of the dose escalation afforded by brachytherapy may be superior to that of EBRT alone.19 The integration of CT and MRI into treatment planning and post-brachytherapy implant assessment, which is now standard practice for some tumor sites, allows more precise delineation of tumor and a better understanding of the exposure of tumor and normal tissue to radiation.20,21 Real-time planning, in which the dose is calculated during the implantation procedure, provides increased flexibility to deliver the radiation dose where desired, with minimal exposure of normal tissues. Today, brachytherapy plays a major role in the treatment of several cancers, including prostate and gynecologic cancers.

**Using Combination Therapy to Reduce the Intensity of Radiotherapy**

For some cancers, such as early-stage Hodgkin’s disease, radiotherapy has long been successful in contributing to disease control, although concerns about late side effects, including second cancers, have prompted efforts to reduce the intensity of radiotherapy. With the introduction of effective, less toxic systemic therapy, radiotherapy treatment volumes have consistently been reduced from classic “extended fields,” which included uninvolved nodal regions, to much smaller regions of nodal involvement and to even smaller involved sites (Fig. 3). Similarly, the doses delivered have been decreased over time, potentially further reducing the risk of late radiation toxicity. Reduced-intensity or reduced-volume radiotherapy has also been used in other clinical scenarios, such as partial breast irradiation in selected patients. Because the long-term effects of treatment may take years to become manifest, the magnitude of any benefit with respect to late toxicity from these modified treatment regimens has yet to be fully defined. Similarly, the side effects of surgery and chemotherapy must be taken into account to ensure that the composite therapy yields an overall benefit in terms of both disease control and reduced toxicity.25,26

**Enhancing the Response to Radiotherapy**

Radiation from external or implanted sources interacts with tissues in a way that drugs simply cannot because it is not bound by bioavailability,
permeability of blood vessels, excretion, or metabolism. The ability to deliver a consistent dose of radiation from an external or implanted source is constrained primarily by the laws of physics. Nevertheless, some tumor types or even regions within tumors may have reduced sensitivity to the tumoricidal effects of radiation, through mechanisms such as hypoxia and accelerated repopulation of tumor cells during treatment, potentially resulting in a reservoir of resistant tumor capable of surviving radiotherapy.

Targeting tumor resistance to radiotherapy has long been a goal in the field of radiation oncology. Methods of enhancing antitumor effects have included accelerated fractionation and hyperfractionation of the radiation dose, so that the killing effects on tumor exceed those on normal tissues. Both approaches generally involve a shorter period of treatment in order to prevent accelerated tumor-cell regrowth, which can occur with more prolonged treatment. These methods have been found in some cases to improve local control and survival.

An alternative method of increasing the efficacy of radiotherapy involves delivery of agents that may enhance the treatment response. In the 1990s and early 2000s, a wealth of data from randomized trials suggested that concurrent use of systemic chemotherapy and radiotherapy can increase local control and, in some situations, survival. Combined chemotherapy and radiotherapy have also provided an opportunity to preserve organs that otherwise would have been surgically removed, such as the larynx and bladder. The benefits of combining these treatments have not been without cost. In some cases, the addition of chemotherapy has increased the risk or severity of treatment side effects, such as dermatitis, diarrhea, and hematologic toxicity. Nevertheless, the consistently enhanced efficacy of treatment with this combined approach in randomized trials has led to the use of concurrent chemoradiation as a cornerstone of care for diverse cancers, such as locally advanced gynecologic cancers and head and neck, gastrointestinal, brain, and thoracic cancers.

Despite the improvements in disease control afforded by technical advances in radiotherapy and the addition of chemotherapy, the search continues for agents that can provide similar or greater radiation-induced tumor-cell killing with reduced toxicity. Radiation not only damages the DNA of cancer cells but also initiates an array of prosurvival, inflammatory, and mitogenic signal-transduction pathways. As a growing number of inhibitors of signal transduction and DNA repair have been developed, a tremendous opportunity has emerged for selectively sensitizing tumors to irradiation through targeting of these pathways. The goal of these endeavors is to develop agents that can be used to enhance the efficacy of radiation delivered to the tumor while minimizing additional toxicity. Several ongoing clinical trials, ranging from phase 1 to phase 3, are investigating radiation sensitizers serving as an alternative or addition to radiosensitizing chemotherapy for the treatment of various tumors and tumor sites.

More recently, the impressive successes of immunotherapy in the treatment of metastatic cancer have led to tremendous excitement at the prospect of combining immunotherapy and radiotherapy. Preclinical studies have suggested that localized irradiation has immunomodulatory effects that may enhance tumor recognition. Compelling evidence of the efficacy of radiotherapy as a complement to immunotherapy has been observed with vaccines. More recently, it was observed that delivery of radiation in combination with antibodies against cytotoxic T-lymphotye–associated antigen 4 (CTLA-4) resulted in regression of unirradiated tumors (known as an abscopal response), providing proof of concept that this approach can be successfully translated into use in patients.

The underlying mechanisms by which radiotherapy enhances immune recognition and may complement immunotherapy are complex and the subject of intensive study (Fig. 4). Radiation-induced injury and killing of tumor cells result in immunogenic modulation and immunogenic cell death. In immunogenic modulation, cell-surface molecules are altered and soluble factors are elaborated in a fashion that enhances tumor antigen presentation to T cells. Immunogenic cell death is characterized by localization of calreticulin and other endoplasmic reticulum proteins at the cell surface. Simultaneously, the release of tumor-cell DNA, ATP, and high-mobility group box 1 (HMGB1), a chromatin-associated protein, from irradiated tumor cells can trigger an immune response through activation of dendritic cells and enhanced antigen pre-
sentation.\(^{36,37}\) Although radiation has the capacity to enhance the immunogenicity of tumors, the observed effects are not capable of stimulating a coordinated and effective immune response by themselves, since abscopal tumor responses to localized palliative radiotherapy as a single treatment approach are rarely observed.

A number of immunosuppressive effects of localized irradiation have been described that may counteract the immunogenic effects, especially when conventionally fractionated radiation or larger treatment volumes that can result in lymphopenia are used.\(^{38,39}\) Radiation can alter the balance of regulatory T cells and local immunomodulatory cytokines, such as transforming growth factor β (TGF-β).\(^{40}\) These changes may suppress antitumor immunity. In addition, radiation may alter the number and phenotype of infiltrating macrophages, which may also serve as an immunosuppressive factor.\(^{41,42}\) Thus, radiation alone may not be capable of stimulating a coordinated and effective immune response.

A number of variables must be considered for effective clinical use of combined radiotherapy and immunotherapy,\(^ {43}\) including the total radiation dose,\(^ {31,44}\) dose fractionation,\(^ {44-46}\) sequencing of immunotherapy, types and combinations of immunotherapeutic agents, and underlying tumor and host factors. These variables are being studied in preclinical models, but their applicability to human tumors is unclear. The optimal dose fractionation may require a balance between initiating immunogenic cell death and minimizing the immunosuppressive effects of hypoxia and vascular collapse seen with higher doses.\(^ {42}\)

Alternative forms of radiation delivery, such as the administration of radiopharmaceutical agents, which have shown tremendous promise in the treatment of metastatic prostate cancer,\(^ {47}\) are also being explored in this context. More than 100 registered clinical trials are attempting to

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**Figure 4. Radiation as an Immune Modulator.**

A simplified depiction of the immune effects of localized irradiation is shown. Radiation can affect the immune state of a tumor in many ways. Irradiation of tumor vasculature can result in expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1). Irradiated tumor cells increase the expression of major histocompatibility complex class I (MHC-I) and Fas. Tumor antigens are released from dying tumor cells, and injured and dying cells may translocate calreticulin to the cell surface. Factors that can activate dendritic cells, such as damage-associated molecular patterns (DAMPs), high-mobility group box 1 protein (HMGB1), and ATP, are also released from irradiated tumor cells. Dendritic cells present tumor-cell antigens to naive T cells, facilitating their conversion to cytotoxic effector cells, which may recognize tumor cells, a process that may also be enhanced by increased MHC-I expression. These events may be highly dependent on the radiation dose, target, and volume and may vary as a function of time after radiation exposure.
Figure 5. Senescence in Cancer Therapy.

Cancer treatments may damage DNA and result in oxidative stress, which can kill tumor cells but can also kill or injure adjacent normal cells. Normal-tissue stem cells are susceptible to therapy-induced senescence. Senescent cells elaborate a complex mixture of cytokines known as the senescence-associated secretory phenotype (SASP), which may enhance inflammation and modify immune phenotypes, stimulate tissue remodeling, and induce senescence in additional normal stem cells, leading to parenchymal depletion. With incomplete tumor regression, senescent noncancerous cells may stimulate the growth of remaining tumor cells.
realize synergy between radiation and immunotherapy (as indicated by a search for the two terms on the ClinicalTrials.gov website).

**UNDE RSTAND ING AND TREAT ING RADIATION TOXICITY**

As with any cancer therapy, radiation treatments can have short-term and long-term side effects that limit treatment tolerability and affect the quality of life. A growing appreciation of the importance of patient-reported outcomes in assessing the toxicity of cancer therapy has led to the development of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events. The rates of moderate and severe toxicity from radiotherapy have consistently decreased over the past several decades as a direct consequence of refinements in imaging, treatment planning, and treatment delivery. For many common cancers, such as breast and prostate cancers, severe late toxicity attributable to radiotherapy occurs infrequently. The site of treatment and type of tumor often drive this risk of injury, with higher rates of toxicity observed when curative doses may approach the tolerance of surrounding normal tissues.

The radiobiologic understanding of normal tissue injury, especially the molecular events leading to injury, has evolved in a fashion analogous to the technological advancements in treatment delivery. Pathways implicated in radiation injury present fresh opportunities for prevention, mitigation, and treatment. An example of such an identified pathway is senescence in normal-tissue stem cells, with accelerated aging as a consequence of cancer treatment. Cellular senescence, which is a normal consequence of aging, can result from DNA damage, oxidative stress, and chronic inflammation. Senescent stem cells are unable to replenish themselves and injured cells; they may also contribute to disease through the secretion of proinflammatory factors, a phenomenon known as the senescence-associated secretory phenotype (Fig. 5). Laboratory studies have confirmed the importance of senescence as a cause of radiation toxicity in bone marrow and lung and of toxicity from DNA-damaging chemotherapy. Additional work has suggested that the factors elaborated by senescent cells may contribute to tumor progression. These findings are of particular interest because of the observed toxic effects and frailty that are consistent with accelerated aging in bone marrow transplant recipients and patients who have received cancer therapy. Preventing or clearing senescent cells has recently been shown to reduce the toxicity of radiation and to mitigate aging-related illnesses in animal models. These studies provide great hope that the short- and long-term toxic effects of radiotherapy and cancer therapy can be effectively mitigated.

A variety of immunomodulatory, profibrotic, and proinflammatory cytokines are also known to be involved in the initiation and perpetuation of radiation injury — most notably, TGF-β. Targeting these molecules and pathways to mitigate radiation toxicity is an area of active study. There is renewed interest in developing agents that can simultaneously sensitize tumors to radiation and reduce the likelihood of long-term radiation injury. Given that several of the pathways involved in these processes overlap, it is highly likely that therapeutic agents will continue to be evaluated in this context.

**CONCLUSIONS**

A rapid evolution of technology has progressively increased the safely deliverable radiation dose, minimized exposure of uninvolved normal tissue, increased the accuracy of tumor delineation, and substantially reduced the expected toxicity of treatment. As a consequence, the toxicity of radiotherapy has consistently decreased, and escalated radiation doses have, in many cases, led to improvements in disease control. Efforts to increase the efficacy of therapy and minimize the risk of injury from radiation treatment continue to evolve.

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