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REVIEW ARTICLE

Effects of Radiotherapy in Normal Tissue

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SUMMARY

Radiotherapy is a key foundation of oncologic treatment that is used across the spectrum of cancer indications. Advances in imaging, treatment planning, and dose delivery have led to increasingly conformal and even ablative treatments, which have resulted in improved tumor control with no increase in the risk of side effects (or with a decrease in risk) as compared with previous treatments. These advances have facilitated the combined use of radiotherapy with efficacious systemic therapies, including targeted treatments and immunotherapies. Radiation-induced changes in normal tissue occur as a result of stem-cell senescence, inflammation, vascular changes, fibroblast activation, and loss of parenchymal cells. Research into the biologic underpinnings of radiation-induced changes in normal tissue, biomarkers of side effects of various irradiation regimens, and new treatment methods offers great promise for further increasing the efficacy of radiotherapy and improving the side-effect profile through personalized approaches.

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RADIOTHERAPY IS THE SECOND MOST COMMONLY USED TREATMENT FOR cancer (after surgery), with oncologic indications that span primary, regional, and metastatic disease and treatment intended to achieve a cure, prolong survival, or provide palliation. Radiation is delivered as a single treatment approach or with other therapies in an effort to control local disease. Throughout most of the history of radiotherapy, small daily dose "fractions" were used to mitigate the side effects from the use of large treatment fields, which included a considerable amount of normal tissue. Recent technological advancements have facilitated the deposition of high doses of radiation in markedly reduced volumes around gross tumor, which allows for the delivery of more ablative doses and results in a considerably higher likelihood of tumor control. Whether radiotherapy is delivered with curative or palliative intent, the goal is to noninvasively control gross or microscopic disease with limited effects in surrounding normal tissues. As with any cancer therapy, side effects are observed in some patients treated with radiotherapy. With an increasing prevalence of long-term survival among patients with cancer,[1] understanding, managing, and reducing the effects of radiotherapy on benign tissues are of critical importance and warrant continuous reexploration and consideration.

MANIFESTATIONS AND PREDICTORS OF SIDE EFFECTS OF RADIOTHERAPY

The expected side effects of a radiotherapy course are at the forefront of every discussion about the risk and benefit of treatment and have a major role in radiotherapy planning and dosing. Low-grade side effects are common during or after a course of therapeutic irradiation, and although these side effects may affect the quality of life, they can often be effectively managed. In contrast, moderate-to-severe late side effects are less common, more difficult to predict, and in some cases more challenging to treat. Although severe side effects occur infrequently, referring physicians, radiation oncologists, and patients should consider them in the context of potential harm from the tumor. Underuse and refusal of indicated radiotherapy have been shown to increase cancer-specific mortality and the risk of death in both curative and palliative settings.[2-4] Thus, understanding, preventing, and treating radiation-related side effects are critical for improving cancer care.

Acute side effects of radiation occur during or shortly after radiation treatment and are more commonly seen when treatment volumes are expanded to prophylactically treat regions at risk for microscopic disease. Acute side effects such as mucositis and dermatitis can result in treatment interruption, which may reduce the efficacy of radiation treatment.[5-8] Although impactful, the acute side effects of radiotherapy are generally time-limited, with resolution occurring within several weeks. Acute effects in normal tissue can be a consequence of the depletion of stem cells in organs or tissues, such as intestinal mucosa, or may be related to acute inflammatory reactions induced by radiation, such as pneumonitis.

Late radiation effects in normal tissues appear months to years after the completion of treatment, often after a latent period that follows the resolution of acute side effects. Some late radiation effects, such as dermal fibrosis and lymphedema, may be chronic in nature and related to the use of large treatment volumes. Late radiation effects are associated with vascular injury, distorted tissue architecture, chronic inflammation, and diminished function of affected tissues and organs. Late effects of focal, high-dose, ablative treatments are feared but fortunately are infrequent, probably owing to the smaller treatment volumes used in these approaches than in conventional radiotherapy.[9] The risks of acute and late side effects depend on the volume of tissue irradiated, the fractional dose of radiation, and the total dose and are therefore correlated.[10,11] However, the presence or absence of acute effects does not guarantee the presence or absence of late effects in the same organ or the same patient.

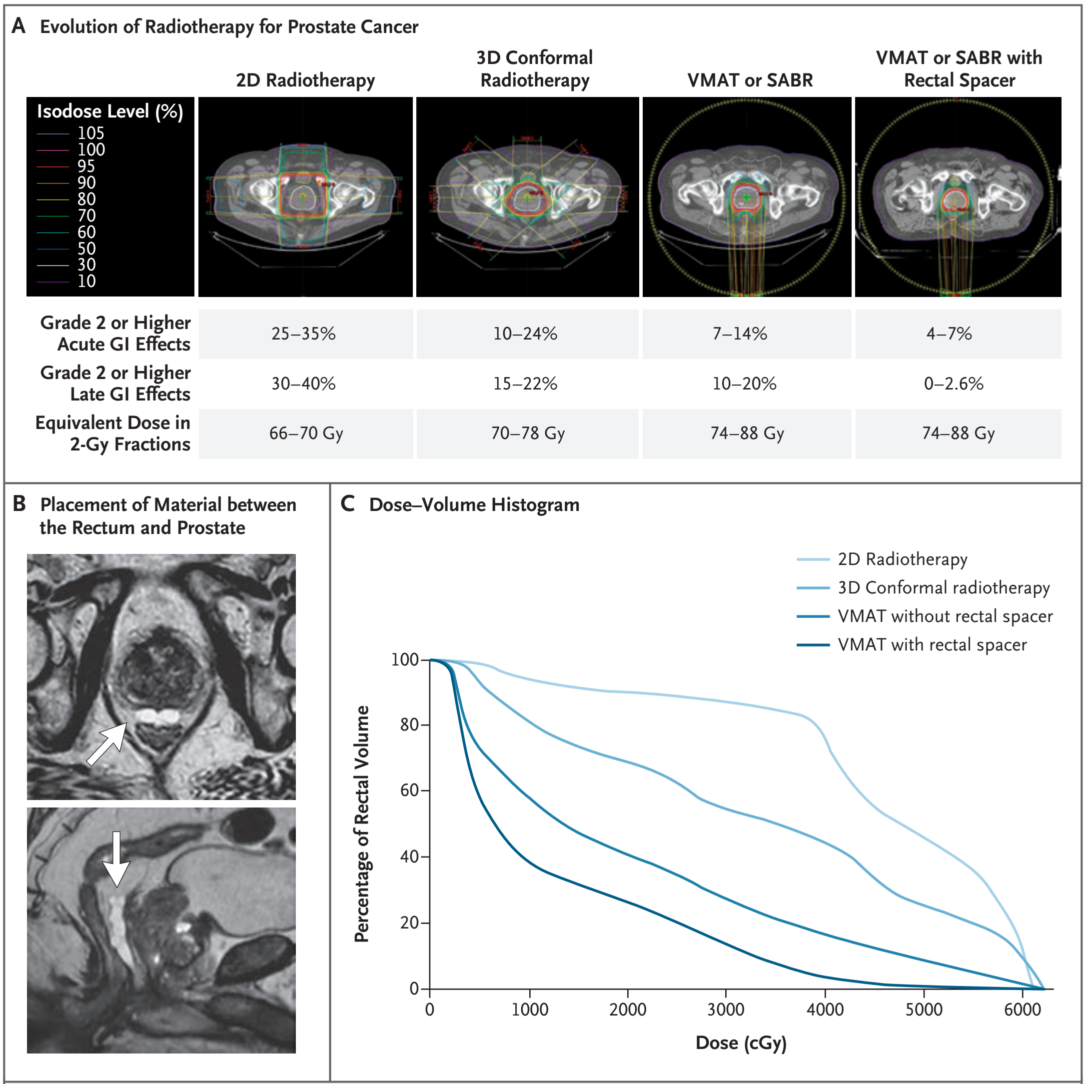
Although systemic side effects, such as fatigue, can occur with localized radiotherapy, the majority of radiation side effects occur in tissues that harbor or are adjacent to tumors in regions that receive the highest radiation dose. The risk of radiation effects in normal tissues increases with larger treatment volumes and higher radiation doses. The risk of side effects is also increased in the context of coexisting conditions, reduced function of the exposed organ, impaired wound healing, previous surgical manipulation of the exposed tissue, genetic predisposition syndromes, and concurrent use of radiosensitizing chemotherapy. The patient's age at the time of exposure may contribute to the risk of side effects in the central nervous system.

The effects of radiation dose, volume, and fractionation on specific organs and tissues vary greatly. Radiation dose constraints for organs and tissues are specific to the fractionation scheme used, are dependent on the tissue volume exposed to a given dose, and, in some cases, are specific to the region or substructure of an exposed organ. Many radiation dose constraints intended to avoid tissue or organ injury were empirically derived and have been continuously modified on the basis of emerging clinical data.

ADVANCES IN RADIOTHERAPY

Advances in the planning and delivery of radiation treatments have come from efforts to simultaneously reduce negative effects in normal tissues and enhance tumor control (Fig. 1). Historically, two-dimensional radiotherapy treatment fields were designed with the use of fluoroscopic images and based on typical anatomy relative to skeletal landmarks. The introduction of computed tomography and other volumetric imaging techniques ushered in an era in which tumor location and extent were more accurately identified. Volumetric imaging also spurred the development of three-dimensional treatment planning to improve the conformality of high-dose regions to tumor and to predict the risk of negative effects in individual organs through analysis of the volume of tissue in which threshold doses and dose or volume limits would be exceeded. These advances provided a markedly improved capacity to predict and reduce the risk of severe effects in normal tissue in an individual patient before the initiation of a course of therapy.

The development of intensity-modulated radiotherapy (IMRT) and its subcategory, volumetric-modulated arc therapy (VMAT), allowed the prescription dose to "bend" into concavities on the



	2D Radiotherapy	3D Conformal Radiotherapy	VMAT or SABR	VMAT or SABR with Rectal Spacer
Grade 2 or Higher Acute GI Effects	25–35%	10–24%	7–14%	4–7%
Grade 2 or Higher Late GI Effects	30–40%	15–22%	10–20%	0–2.6%
Equivalent Dose in 2-Gy Fractions	66–70 Gy	70–78 Gy	74–88 Gy	74–88 Gy

Figure 1. Evolution of Radiotherapy for Prostate Cancer and Gastrointestinal Effects.

Panel A shows the evolution of radiotherapy for prostate cancer from two-dimensional (2D) radiotherapy to three-dimensional (3D) conformal radiotherapy to intensity-modulated radiotherapy with the use of volumetric-modulated arc therapy (VMAT) or stereotactic ablative radiotherapy (SABR). Representative axial images for treatment planning are shown (the thick white lines indicate the prostate). Both intensity-modulated radiotherapy and SABR are commonly used treatments in contemporary radiation oncology. The expected incidence of grade 2 or higher acute or late adverse effects involving the gastrointestinal (GI) system — typically, proctitis or rectal bleeding — is based on data from multi-institutional and cooperative-group trials.[11-17] Grade 3 rectal adverse effects are rare (incidence, <1%) with contemporary prostate radiation treatments. Placement of material that creates space between the rectum and prostate has further facilitated a reduction in the radiation dose to the rectum when the prostate and seminal vesicles are the intended radiation target. Representative axial and sagittal images from magnetic resonance imaging after spacer placement are shown in Panel B (arrows indicate spacers). The dose–volume histogram in Panel C shows the percentage of the rectum exposed to each dose for the four treatment plans in Panel A, assuming that the intended dose to the target area is equal in the four plans.

tumor target and avoid abutting normal tissues. The advent of IMRT was soon followed by motion-management techniques designed to decrease or account for organ motion during treatment in order to further reduce the margin of normal tissue that must be treated to ensure adequate tumor coverage. Integration of magnetic resonance imaging (MRI) and functional imaging techniques, such as fluorodeoxyglucose–positron-emission tomography (FDG-PET), further enhanced confidence in tumor delineation and allowed a reduction in the volumes of clinically uninvolved tissues that were treated electively, without a compromise in efficacy for many tumor types.

Advances in targeting, localization, and delivery of radiation enabled the evolution toward definitive hypofractionated and ultrahypofractionated radiotherapy regimens, in which the radiation dose is delivered in fewer and larger fractions. Although these regimens were historically taboo because of the hypothesized higher risk of late effects, the oncologic and safety outcomes have compared favorably with those of conventional fractionation (1.8 to 2.0 Gy per fraction), and these regimens are now considered standard treatment options. Ultrahypofractionated treatments, such as stereotactic radiosurgery in the brain and stereotactic ablative radiotherapy at other body sites, typically target only visible disease and are now commonly used for localized disease and metastatic deposits.

Most of the innovations described were developed for x-rays (photons), the most commonly delivered form of external-beam radiotherapy. Positively charged particles, such as protons and heavier ions, deposit a modest dose on entry into the tissue, with a dramatic release of the dose at a depth that is based on the particle mass and energy (the Bragg peak), and no exit dose. Therefore, the use of charged particles has the potential to improve the distribution of the radiation dose, as compared with the use of photons. The properties of positively charged particles have been used to reduce negative effects of radiation in normal tissues, particularly in vulnerable pediatric populations, or to increase the dose at an equivalent risk of side effects for radioresistant tumors such as chordoma. Several ongoing clinical trials are attempting to define the effectiveness of proton therapy relative to photon-based radiotherapeutic approaches by assessing oncologic outcomes, side effects, and patient-reported symptoms (ClinicalTrials.gov numbers NCT05055648, NCT03186898, NCT06500481, NCT01617161, and NCT02603341).

These transformational advances in radiotherapy planning and delivery have occurred in the context of the increasing efficacy of systemic therapy for many malignant diseases. In previous decades, elective radiotherapeutic treatment of grossly uninvolved regions at high risk for metastatic spread, such as regional nodal basins, was a common approach. The availability of more independently effective systemic therapies, coupled with the ability to use radiotherapy to more precisely treat visible disease and spare grossly uninvolved tissue, has led to an approach that capitalizes on the concept of spatial cooperation,[18] in which effective systemic therapy is followed by radiotherapy to a reduced volume of tissue that is at highest risk for progression or recurrence. The efficacy of this approach and the reduction in side effects of radiation that occurs with reduced treatment volumes have been clearly shown.[19,20]

Systemic radiopharmaceuticals, such as iodine-131–labeled sodium iodide ($\mathrm{Na^{131}I}$), radium-223 dichloride ($\mathrm{^{223}RaCl_2}$), lutetium-177 ($\mathrm{^{177}Lu}$)–oxodotreotide, $\mathrm{^{177}Lu}$-PSMA-617, and $\mathrm{^{131}I}$-metaiodobenzylguanidine ($\mathrm{^{131}I}$-MIBG), are established treatments for some metastatic and high-risk cancers. Radiopharmaceuticals are being investigated as an adjunct to external radiotherapy, brachytherapy, immunotherapies, targeted agents, and systemic chemotherapy. Factors that must be considered in determining the effects of systemic radiopharmaceuticals in normal tissue include the type of radionuclide, the mechanism of clearance (renal or hepatic), and off-target effects (e.g., effects on salivary glands with $\mathrm{Na^{131}I}$ and $\mathrm{^{177}Lu}$-PSMA-617). Estimation of the absorbed dose (dosimetry) in normal tissue with the use of post-treatment serial imaging may allow a more precise estimation of effects in normal tissue and facilitate patient counseling about the risk of specific effects.[21]

INCIDENCE OF SIDE EFFECTS OF RADIOTHERAPY

The advances in radiotherapy have markedly altered the observed and expected incidence of side effects from a prescribed course of treatment. A reduction in the incidence of side effects from radiation over time is probably the result of multiple factors, including reduced treatment volumes, increased conformality, the adoption of motion management and daily image guidance for treatment, and avoidance of non–tumor-selective, radiosensitizing drugs, particularly with hypofractionation. The benefits of these changes have been realized in the treatment of many cancer types.

One example of this trend is the treatment of some lymphomas, for which radiotherapy has evolved from total nodal irradiation to mantle-field irradiation to involved-field irradiation (treatment of regional lymph-node basins) to involved-site irradiation (treatment restricted to the site of visible disease).[20] The volume of clinically uninvolved tissue exposed to radiation and potential complications has thus been markedly reduced over time. Similarly, the dose of radiation used to sterilize these sites has been reduced as systemic therapy has proven more effective.[22] The use of IMRT and other conformal approaches has further reduced the amount of uninvolved tissue exposed to the prescription dose. Collectively, these advances in radiotherapy and systemic therapy have resulted in a substantially reduced incidence of side effects over the past three decades (Fig. 1).[11-17,23-26]

Reduction of the treatment dose and volume has altered care for cancers other than lymphoma, such as human papillomavirus–positive head and neck cancers, non–small-cell lung cancers, and early-stage breast cancer. In these contexts, IMRT has enhanced dose conformality and allowed maximal sparing of sensitive normal tissues. Although IMRT minimizes the amount of normal tissue exposed to the prescription dose, larger volumes of normal tissue are exposed to low doses of radiation with IMRT than with older two- and three-dimensional approaches; concern that this exposure would increase the incidence of second cancers[27] has not been borne out.[28] The proliferation of ultrahypofractionated approaches, such as stereotactic body radiotherapy, has enhanced the convenience of radiotherapy; however, this new technique also generated concern about severe side effects when it was first introduced.[9,29] Data from substantial clinical experience, including numerous prospective trials, now support the relative safety and efficacy of stereotactic body radiotherapy for multiple primary and metastatic sites. Radiotherapy is often used concurrently with radiosensitizing chemotherapy and will most likely continue to be delivered along with new and established systemic therapies. While these opportunities are explored, the possibility of an unexpected interaction that could exacerbate effects in normal tissue must be considered.

BIOLOGIC UNDERPINNINGS OF SIDE EFFECTS OF RADIATION

Radiobiologic models developed with the use of characteristics such as mitotic capacity, tissue hierarchy, and differentiation state can predict responses in normal tissue at the levels of the cell, tissue, and organ.[30,31] For example, the interaction of the dose and volume of radiation with the risk of effects in normal tissue is tissue- or organ-specific and dependent on the organization of the smallest functional subunits (e.g., nephrons, neurons, or alveoli) within the tissue.[32] For some organs in which the functional subunits are organized in parallel (e.g., nephrons in the kidney), approximately a third of the total volume of the organ must be spared from receiving a relatively low threshold dose to maintain functional organ viability. The remaining two thirds of the organ constitutes a functional reserve. In contrast, when functional subunits are arranged in series (e.g., spinal cord neurons), even a focal injury threatens organ function (e.g., spinal cord myelopathy). Tissues with parallel organization generally have a higher tolerance for radiation than tissues with serial organization. Ablative treatments such as stereotactic ablative radiotherapy are more likely to have an acceptable safety profile when applied in and around tissues with parallel organization or in tissues capable of compensatory hyperplasia after injury than in serially functioning tissues (Fig. 2).

Our understanding of the biologic events underlying the initiation and progression of side effects of radiation has grown rapidly in recent decades and is built on the foundation of classical radiobiologic models (Fig. 3). In the moments after radiation exposure, the energy of the treatment is absorbed in the irradiated tissue, which results in direct damage to cellular components and additional, indirect damage from reactive oxygen species formed from ionization events.[33] Although this damage affects many cellular components, the formation of double-strand breaks in DNA that remain unrepaired is considered to be a key lethal event. The initial damage that occurs after irradiation is accompanied by the release of damage-associated molecular patterns (DAMPS), activation of numerous signal transduction pathways, and other host responses that acti-

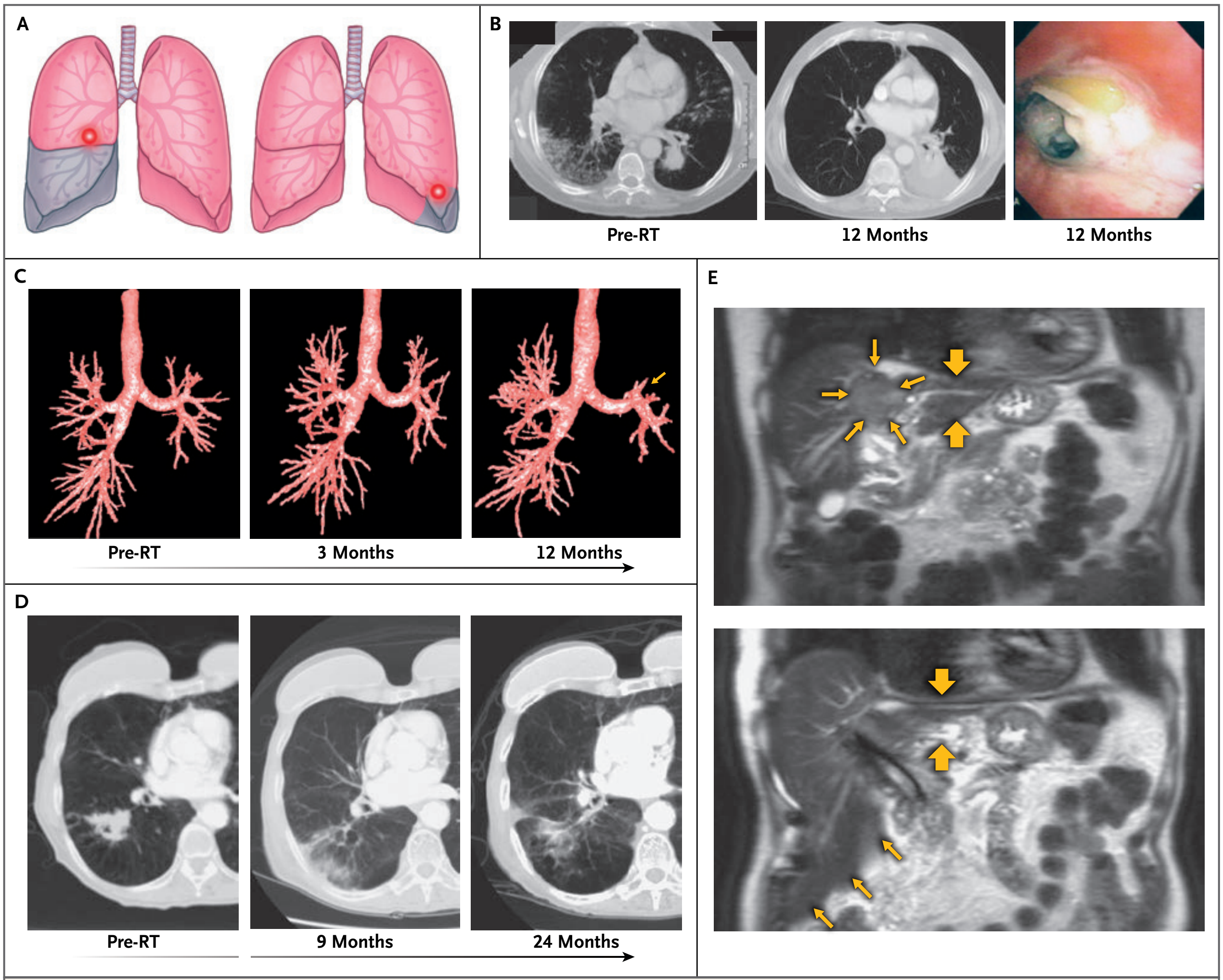


Figure 2. **Effects of Radiotherapy and Organ Repair in Tissues with Serial and Parallel Organization.**

As shown in Panel A, the lung is composed of branching airways and alveoli. The airways are arranged in series (left-hand image), such that when an ablative dose is delivered to a portion of the airway (red and white sphere), the airway is obstructed and distal airways and alveoli collapse (gray area). When more-peripheral portions of the lung are targeted (right-hand image), only the terminal airways and associated alveoli, which are arranged in parallel, are damaged (gray area). In Panel B, a pretreatment computed tomographic (CT) image shows a central non–small-cell lung cancer posterior to the left hilum (left-hand image; identifying information is masked), with an unrelated right-lower-lobe infiltrate. A CT image obtained 12 months after delivery of 50 Gy in 5 fractions shows complete collapse of the superior segment of the left lower lobe, with a focal pleural effusion (middle image). A bronchoscopic view of the superior-segment airway shows intense mucositis with obstructive debris (right-hand image). Panel C shows virtual bronchoscopic reconstruction in a patient with locally advanced non–small-cell lung cancer that was treated with 60 Gy in 30 fractions. A post-treatment decline in pulmonary function was attributed to radiation. Pretreatment virtual bronchoscopic reconstruction of airways showed a baseline paucity of viable airways on the left side. Imaging at 3 months after radiotherapy showed mild worsening of airway patency in the left lung, which was followed by substantial worsening at 12 months (arrow). Panel D shows serial CT images from a patient with stage IB non–small-cell lung cancer treated with 54 Gy of radiation delivered to the superior segment of the right upper lobe in 3 fractions. Pretreatment imaging showed a large, lobulated lung tumor. Images obtained 9 and 24 months after radiotherapy showed a complete response of the treated tumor, with wedgelike atelectasis. Panel E shows tissue repair after radiation injury. The coronal view (top) shows a large colorectal liver metastasis (thin yellow arrows), with an intact left lobe (wide yellow arrows). The metastasis was treated with 60 Gy delivered in 5 fractions. An image obtained after treatment (bottom) shows a complete response of the treated tumor, with radiation-related amputation of the entire left lobe of the liver, which resulted from injury of the serially functioning ducts and blood vessels (wide yellow arrows). Hypertrophy of the remaining right lobe of the liver (hyperplasia) is evident (thin yellow arrows). Collectively, these findings represent an injury-and-repair response to the ablative radiotherapy used to eliminate the central tumor. Pre-RT denotes preradiotherapy.

vate cytokine and chemokine production, enhance vascular leak, and initiate inflammation. The resulting immune-cell activation, ongoing oxidative stress, cellular senescence, cell death, and matrix production culminate in acute and late effects of radiation. Although normal tissue can be affected by radiation, noncancerous cells have a greater capacity to repair potentially lethal damage than tumor cells, a difference that is magnified when treatment is delivered in multiple fractions.

Acute radiation effects in epithelial tissues, such as skin and intestine, have been attributed to the depletion of rapidly dividing stem cells in normal tissue and the death of mature parenchymal cells, which lead to a loss of barrier function, inflammation, tissue edema, and oxidative stress. Although radiation injury is often described as sterile inflammation, data from recent studies have supported a key role of the host microbiome in determining the severity of acute radiation effects, such as in the case of radiation dermatitis.[34,35] Similarly, acute effects in nonepithelial tissues, such as the central nervous system, are

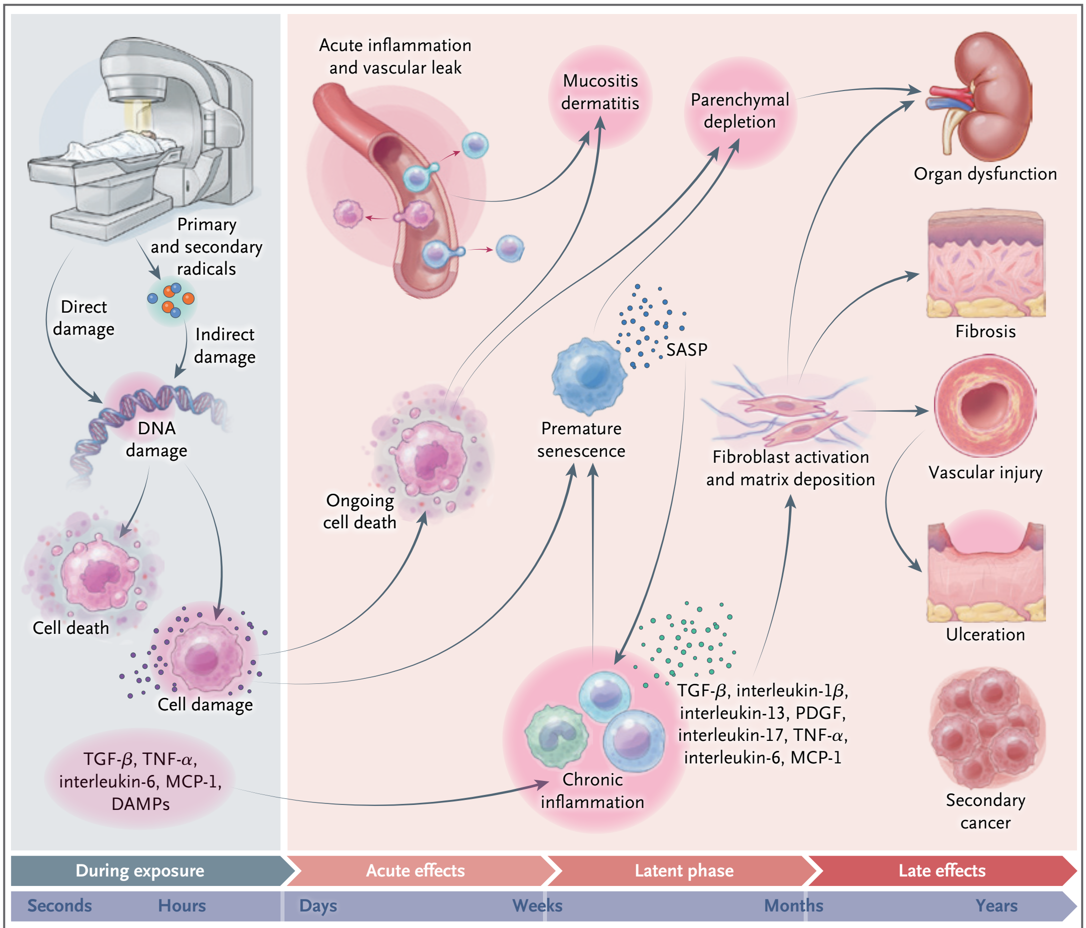


Figure 3. Radiobiologic Processes in Normal Tissue.

Immediately after the exposure of tissue to radiation, numerous events are initiated, including direct damage of cellular components and indirect damage through primary and secondary radicals. Cell death and cell injury initiate the release of numerous cytokines, chemokines, and immunomodulatory molecules, a process that causes acute inflammation and effects in normal tissue. Cells that are damaged by radiation may repair the damage, die, or undergo premature senescence and contribute to chronic inflammation through elaboration of the senescence-associated secretory phenotype (SASP). Collectively, these processes lead to loss of organ function, fibrosis, and other late effects of radiation. DAMPs denotes damage-associated molecular patterns, MCP-1 monocyte chemoattractant protein 1, PDGF platelet-derived growth factor, TGF-β transforming growth factor β, and TNF-α tumor necrosis factor α.

often associated with dysfunction related to inflammation and edema.

Late radiation effects are often attributed to chronic inflammation, inflammation-related oxidative stress, parenchymal depletion due to stem-cell senescence in normal tissue, vascular injury, and fibrosis.[36] Cells that are damaged and killed during the initial exposure must be replaced to maintain tissue homeostasis and function. Inflammation-related oxidative stress and DNA damage result in the senescence of stem cells in normal tissue. These senescent stem cells are incapable of dividing and replenishing parenchymal cells, and as a result, organ function is eventually impaired. In addition, senescent cells in irradiated tissue may contribute to secondary injury and inflammation through the secretion of a mixture of cytokines, chemokines, growth factors, proteases, and immunomodulatory proteins, a phenomenon known as the senescence-associated secretory phenotype, which has been implicated in secondary senescence, initiation and maintenance of radiation-induced inflammation and injury, and tumor growth.[37-42] Data from a growing body of literature support the complex interplay between senescent cells in irradiated tissue and macrophages,[37] which are known to have a key role in the chronic inflammation associated with late side effects of radiation. Preventing senescence and clearing senescent cells have been shown to rejuvenate irradiated tissue and mitigate radiation injury in animal models.[40,43-45] Several agents that target these molecules and pathways are under investigation as therapies for side effects from radiation.

MANAGEMENT OF SIDE EFFECTS OF RADIOTHERAPY

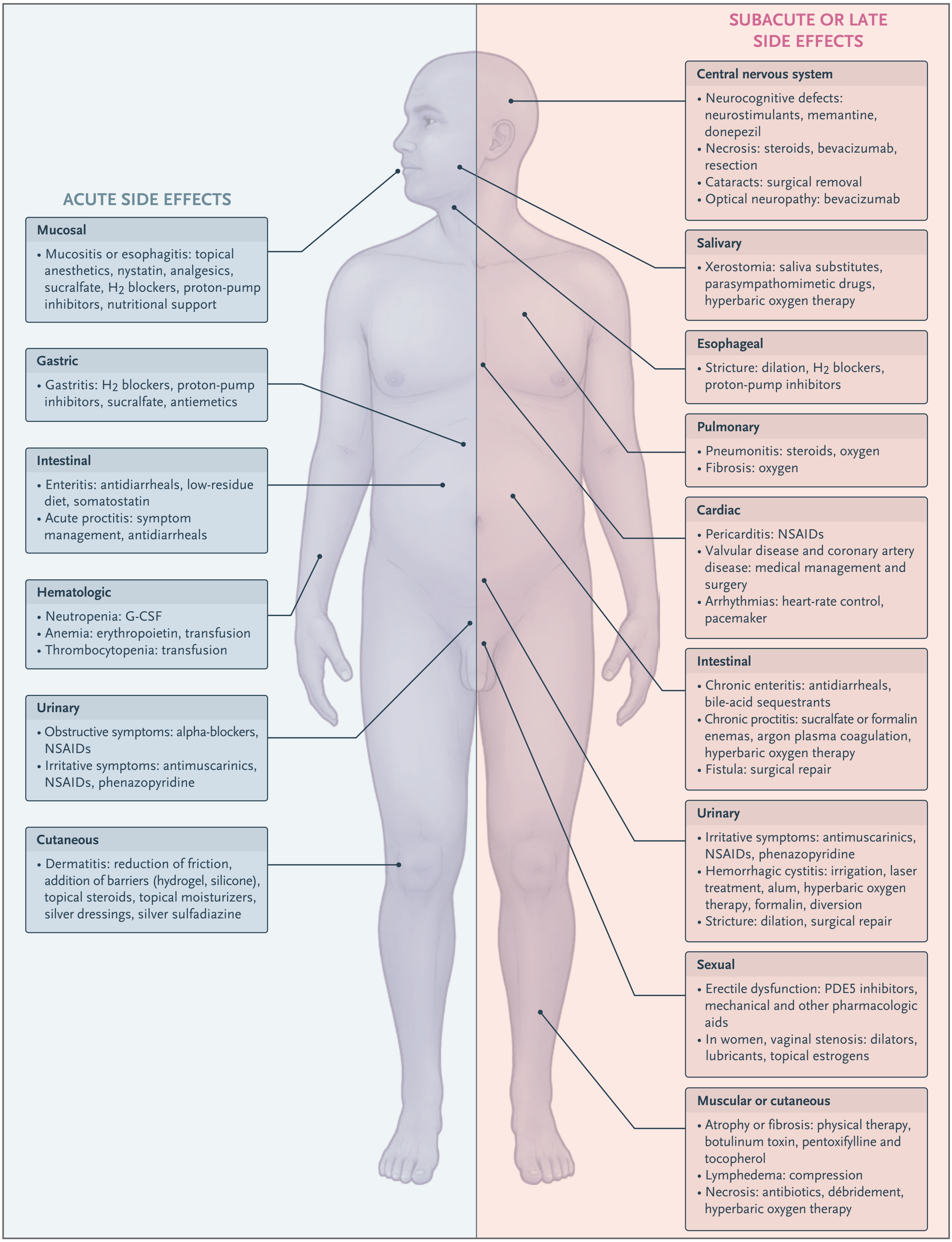
As with any cancer treatment, side effects of radiotherapy are expected to occur in a subgroup of patients, despite precautions. The management of side effects of radiation is often a multidisciplinary effort (Fig. 4). The management of self-limited, acute radiation effects focuses on supportive care, a reduction in inflammation, antibiotic or antifungal treatment when indicated, and symptom management (e.g., pain relief).[46] Early recognition and management of acute radiation effects can improve the patient experience and adherence to treatment.

The management of late radiation effects is also a multidisciplinary effort and is similarly focused on treatment of inflammation and on pharmacologic and nonpharmacologic relief of symptoms, with physical therapy when indicated and surgical intervention when other options fall short. Many late effects of radiotherapy are characterized by fibrosis, vascular damage, and impaired wound healing. Clinical guidelines have been established for the management of several late effects of radiotherapy.[49-54] A number of therapies have shown promise in the treatment of such effects, including repurposed agents,[55,56] cell therapies,[57] and gene therapy.[58] However, these treatments remain investigational.

ADVANCES IN REDUCING SIDE EFFECTS OF RADIATION

Recent advances in radiation oncology are centered on predicting negative effects in normal tissue, increasing the accuracy and precision of treatment, capitalizing on radiobiologic principles, and developing treatments for side effects of radiation. Accurate identification of persons at highest risk for side effects of radiation is an area of intensive research. Radiation sensitivity syndromes, such as the Li–Fraumeni syndrome and ataxia telangiectasia, are uncommon but are known to increase the risk of radiation-related side effects and radiation-induced second cancers.[59] Genomewide association studies have identified genomic regions associated with side effects of radiation,[60,61] and prospective studies investigating assays based on single-nucleotide variants are ongoing.[62,63] In most cases, predicting the likelihood of side effects for an individual patient undergoing radiotherapy is not yet possible beyond known dosimetric correlations and clinical risk factors.

Functional assays have been explored as an alternative method to categorize a patient's intrinsic cellular response to irradiation, with the goal of predicting the risk of side effects. Many of these assays use ex vivo assessments of DNA repair or cell death in lymphocyte subsets or fibroblasts after a test dose of radiation.[64] Researchers have also sought to analyze increases in circulating cytokines, either individually[65] or as a panel, during treatment in order to predict side effects. The proliferation of multiomic assays offers an opportunity to explore multiple biomarkers simultaneously and to incorporate these biomarkers



ACUTE SIDE EFFECTS

Mucosal
- Mucositis or esophagitis: topical anesthetics, nystatin, analgesics, sucralfate, H_2 blockers, proton-pump inhibitors, nutritional support

Gastric
- Gastritis: H_2 blockers, proton-pump inhibitors, sucralfate, antiemetics

Intestinal
- Enteritis: antidiarrheals, low-residue diet, somatostatin
- Acute proctitis: symptom management, antidiarrheals

Hematologic
- Neutropenia: G-CSF
- Anemia: erythropoietin, transfusion
- Thrombocytopenia: transfusion

Urinary
- Obstructive symptoms: alpha-blockers, NSAIDs
- Irritative symptoms: antimuscarinics, NSAIDs, phenazopyridine

Cutaneous
- Dermatitis: reduction of friction, addition of barriers (hydrogel, silicone), topical steroids, topical moisturizers, silver dressings, silver sulfadiazine

SUBACUTE OR LATE SIDE EFFECTS

Central nervous system
- Neurocognitive defects: neurostimulants, memantine, donepezil
- Necrosis: steroids, bevacizumab, resection
- Cataracts: surgical removal
- Optical neuropathy: bevacizumab

Salivary
- Xerostomia: saliva substitutes, parasympathomimetic drugs, hyperbaric oxygen therapy

Esophageal
- Stricture: dilation, H_2 blockers, proton-pump inhibitors

Pulmonary
- Pneumonitis: steroids, oxygen
- Fibrosis: oxygen

Cardiac
- Pericarditis: NSAIDs
- Valvular disease and coronary artery disease: medical management and surgery
- Arrhythmias: heart-rate control, pacemaker

Intestinal
- Chronic enteritis: antidiarrheals, bile-acid sequestrants
- Chronic proctitis: sucralfate or formalin enemas, argon plasma coagulation, hyperbaric oxygen therapy
- Fistula: surgical repair

Urinary
- Irritative symptoms: antimuscarinics, NSAIDs, phenazopyridine
- Hemorrhagic cystitis: irrigation, laser treatment, alum, hyperbaric oxygen therapy, formalin, diversion
- Stricture: dilation, surgical repair

Sexual
- Erectile dysfunction: PDE5 inhibitors, mechanical and other pharmacologic aids
- In women, vaginal stenosis: dilators, lubricants, topical estrogens

Muscular or cutaneous
- Atrophy or fibrosis: physical therapy, botulinum toxin, pentoxifylline and tocopherol
- Lymphedema: compression
- Necrosis: antibiotics, débridement, hyperbaric oxygen therapy

Figure 4 (facing page). Representative Acute, Subacute, and Late Effects of Radiotherapy and Their Management.

Treatment options are based on published guidelines, clinical practice, and published summaries.[46-48] Alum denotes potassium aluminum sulfate, G-CSF granulocyte colony-stimulating factor, H_2 blocker histamine H_2–receptor antagonist, NSAIDs nonsteroidal antiinflammatory drugs, and PDE5 phosphodiesterase type 5.

into models of prediction that include dosimetry and assessment of known risk factors for side effects.

The integration of genomic classifiers, molecular phenotypes, and advanced imaging techniques has helped to ensure that radiotherapy and other adjuvant treatments are used only for the patients who are most likely to benefit from them. Although radiation dosing has historically been dependent on the site, stage, and histologic features of the cancer, personalized approaches based on the transcriptional profile have been used to determine a patient-specific dose of radiation that may be appropriate for maximizing the likelihood of a cure, with the potential benefit balanced against the expected risk of side effects.[66] Advances in data science and data integration provide the opportunity to integrate information from the medical history, imaging, genomics, transcriptomics, and dosimetry in order to develop models capable of defining an appropriate radiation regimen on the basis of the predicted tumor response and effects in normal tissue. Beyond prediction, such modeling may provide future insights into the underlying causes of side effects from radiation.

The most accurate predictor of side effects from radiation is the distribution of the dose in normal tissue, as defined in the treatment plan. This predictive power depends on the reproducibility of the anatomy during treatment sessions relative to the time of planning. Changes in the tumor and the anatomy of normal tissue can occur between radiation treatments (interfraction), as a result of changes in patient position or alignment, weight loss, tumor shrinkage, and variable filling of visceral organs, and during treatment (intrafraction), as a consequence of ventilation, peristalsis, and patient motion. These changes may result in unintended underdosing of the tumor and unanticipated dose "hot spots" in normal tissue. Interfraction motion can be detected and mitigated with daily imaging before treatment delivery and with positional adjustments to align the patient relative to the treatment plan. However, in some cases, particularly with highly conformal IMRT plans and targets adjacent to sensitive normal tissue, the differences between the treatment plan and the anatomy at the time of treatment exceed an acceptable threshold and require a modified treatment plan.

Adaptive radiotherapy involves modifying treatment plans to account for changes in anatomical geometry that are not adequately mitigated with changes in alignment. Online adaptive radiotherapy capitalizes on advances in image guidance, real-time tumor tracking, and the enhanced speed of multiple steps in radiotherapy planning and delivery workflows (Fig. 5). With online adaptive treatment, the treatment plan is modified during the session in which the anatomical or biologic variation is identified.

Online adaptive approaches are resource-intensive and require a rapid workflow for replanning and optimization. Advances in planning, such as autosegmentation, integration of artificial intelligence in treatment planning, and the increasing efficiency of steps required to create, approve, and deliver a new treatment plan, are making online adaptive approaches a more realistic option. Collectively, these adaptive strategies move toward marginless treatments, which allow for a reduction in side effects. Online adaptive approaches now incorporate MRI linear accelerators and PET linear accelerators to facilitate biologic personalization. Biologically adapted radiotherapy involves the use of functional imaging (e.g., assessment of hypoxia and glucose uptake) to guide dose delivery, with the potential to change the treatment plan at each fraction as the functional characteristics of the tumor change. The capacity exists to use these approaches in order to preferentially spare critical normal tissues that show changes that are consistent with early injury.

Personalized ultrahypofractionated stereotactic adaptive radiotherapy (PULSAR) is an investigational approach that integrates stereotactic body radiotherapy and adaptive treatments, with longer time windows between treatment fractions than in traditional approaches.[67] The goal is to capitalize on tumor shrinkage or other biologic changes between fractions in order to minimize breaks in systemic therapy when radiotherapy is indicated[68] and to allow enhanced immune modulation in the context of combined stereotactic body radiotherapy and immune checkpoint inhibition.[67,69] The longer breaks between fractions of radiation may allow for repair of organs and normal tissue, which could potentially reduce the effects of treatment in normal tissues.

FLASH radiotherapy, characterized by the delivery of ultra-high-dose-rate irradiation (>40 Gy per second) in short pulses, appears to offer strikingly selective tumor-cell killing with preferential sparing of normal tissues.[70] The precise mechanism underlying the tumor selectivity of FLASH remains uncertain, although proposed mechanisms include normal-tissue hypoxia and stem-cell hypoxia within normal tissue through radiolysis of water and reduced exposure of immune cells within the blood pool. FLASH irradiation has been delivered to patients in clinical trials and appears to be feasible, with an acceptable safety profile.[71] The benefits of FLASH, PULSAR, and other investigational techniques of radiation delivery relative to standard approaches are uncertain and must be evaluated in clinical trials.

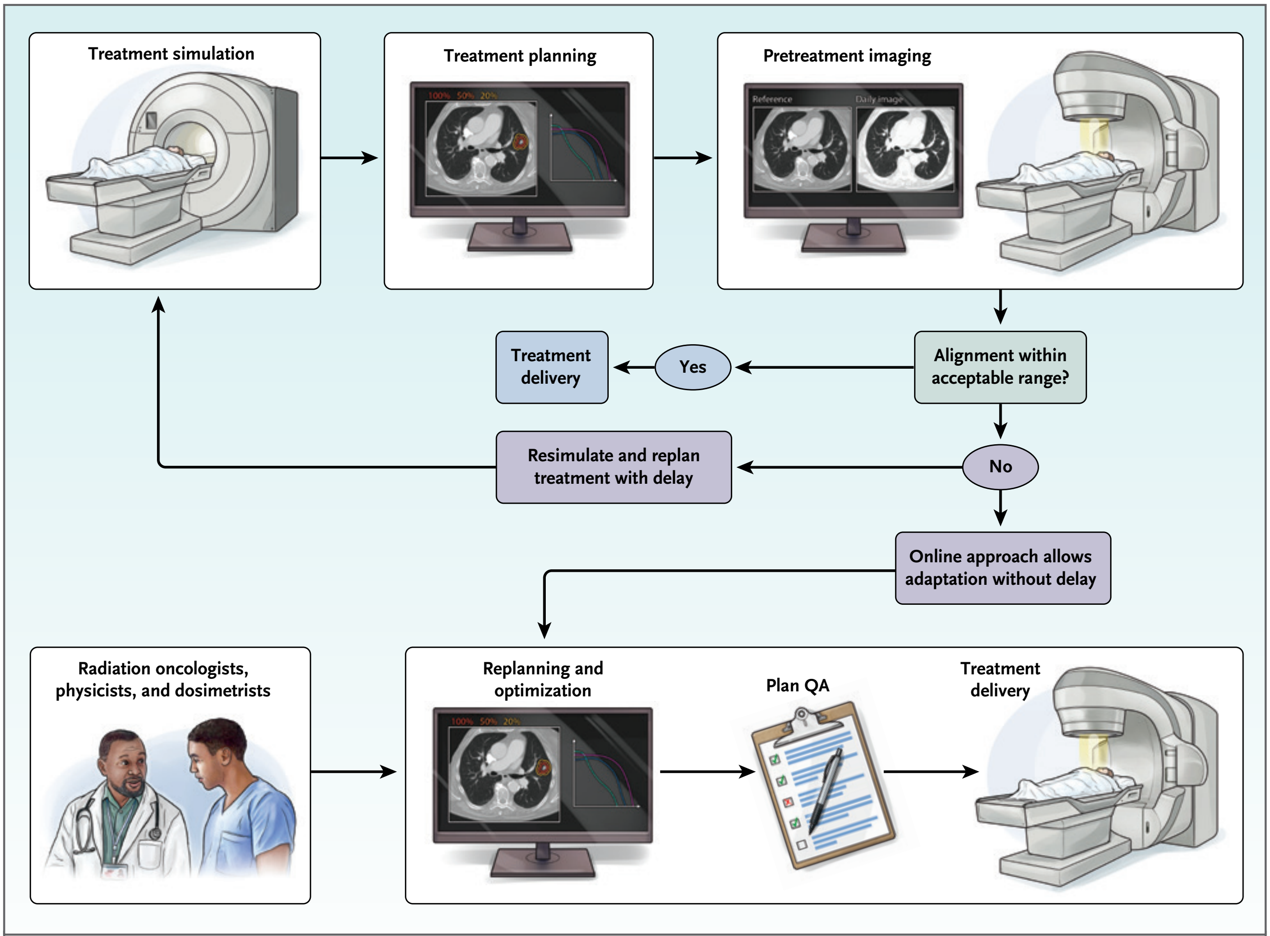


Figure 5. **Online and Offline Approaches to Adaptive Radiotherapy.**

In both online and offline approaches, the patient undergoes a simulation and treatment planning. On the day of treatment delivery, a pretreatment image is obtained and compared with a reference (planning) image. If the alignment is within an acceptable range, the treatment is delivered. If the alignment is outside the acceptable range or if marked anatomical changes are noted, the treatment must be replanned. With online adaptive approaches, replanning and quality assurance (QA) occur while the patient remains on the treatment table, and the new treatment is delivered without delay. Online adaptive approaches are resource-intensive and require real-time availability of radiation oncologists, physicists, and dosimetrists. Offline approaches allow for the care team to prepare a new plan without real-time availability, but a delay or break in the treatment may occur.

KEY POINTS

EFFECTS OF RADIOTHERAPY IN NORMAL TISSUE

- Radiotherapy is a key component of oncologic care for a variety of cancers.
- Innovations in imaging and in delivery of radiation have improved the accuracy and precision of radiation treatments, which has led to marked reductions in the incidence and severity of effects in normal tissues.
- The expected side effects from radiation treatments depend on the dose delivered, the volume of tissue treated, concurrent treatments (e.g., surgery and systemic therapy), and coexisting conditions.
- Our understanding of biologic processes in normal tissue after radiation exposure has deepened in recent years, and several candidate agents have been developed for the prevention, mitigation, and treatment of side effects of irradiation.
- Management of radiation toxicity benefits from multidisciplinary collaboration.

CONCLUSIONS

The field of radiotherapy continues to incorporate new technology and personalized approaches to improve oncologic outcomes while reducing the risk of side effects. With modern innovations that reduce the exposure of uninvolved tissues to radiation, the advent of treatment approaches that prioritize highly conformal ablative dosing only to grossly visible disease, and the availability of treatments for side effects of irradiation, radiation oncologists and collaborating physicians have begun to revisit what is defined as an "acceptable risk" of side effects from radiation, with the emerging concept that allowing otherwise preventable injury or repairable injury to occur may permit more effective treatment and a more favorable overall side-effect profile.[72] Yet radiation oncologists continue to prioritize avoidance of side effects altogether, a strategy that allows radiotherapy to retain its reputation as an effective and safe treatment for a broad scope of malignant conditions.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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