Radiation Therapy-Associated Toxicity: Etiology, Management, and Prevention

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Abstract: Radiation therapy (RT) is a curative treatment for many malignancies and provides effective palliation in patients with tumor-related symptoms. However, the biophysical effects of RT are not specific to tumor cells and may produce toxicity due to exposure of surrounding organs and tissues. In this article, the authors review the clinical context, pathophysiology, risk factors, presentation, and management of RT side effects in each human organ system. Ionizing radiation works by producing DNA damage leading to tumor death, but effects on normal tissue may result in acute and/or late toxicity. The manifestation of toxicity depends on both cellular characteristics and affected organs' anatomy and physiology. There is usually a direct relationship between the radiation dose and volume to normal tissues and the risk of toxicity, which has led to guidelines and recommended dose limits for most tissues. Side effects are multifactorial, with contributions from baseline patient characteristics and other oncologic treatments. Technological advances in recent decades have decreased RT toxicity by dramatically improving the ability to deliver RT that maximizes tumor dose and minimizes organ dose. Thus the study of RT-associated toxicity is a complex, core component of radiation oncology training that continues to evolve alongside advances in cancer management. Because RT is used in up to one-half of all patients with cancer, an understanding of its acute and late effects in different organ systems is clinically pertinent to both oncologists and nononcologists. **CA Cancer J Clin 2021;0:1-18.**

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Introduction

Radiation therapy (RT) is one of the primary modalities for treating malignant diseases and is used in both curative and palliative settings for almost all solid tumors. Commonly combined with surgery, cytotoxic chemotherapy, and immunotherapy, RT is part of first-line cancer treatment in >30% of patients in the United States,[1] and approximately one-half of all patients with cancer will receive RT during their care.[2] An understanding of RT toxicities is pertinent to oncologists, primary care physicians, and other clinicians engaged in cancer treatment, supportive management, and survivorship care. Here, we review the side effects (expected and unexpected) of therapeutic radiation. Of note, there is a separate, broad class of radiation injury secondary to whole-body irradiation from nuclear accidents/weapons termed "acute radiation syndrome." A detailed discussion is beyond the scope of this article, but these include central nervous system (CNS) syndrome (within days at high doses from >20 to 30 Grays [Gy] [1 Gy = 100 rads], gastrointestinal syndrome (within weeks at moderate doses from >5 to 8 Gy), and hematopoietic syndrome (within months at low doses from >1 to 2 Gy).

The mechanism of cell killing from radiation is not selective for tumor cells, and optimal delivery of RT is a balance between maximization of tumor dose and minimization of normal tissue dose. Thus the study of radiation toxicity is a core component of radiation oncology training, and practices are guided by an extensive and evolving literature on factors associated with toxicity probability.[3,4] The study of radiation toxicity is also pertinent to nuclear medicine and the evolving field of "theranostics," in which radionuclides linked to targeting agents have both diagnostic and therapeutic utility, although dosimetric studies on efficacy and toxicity have been limited.[5,6]

Modern advances in external-beam RT delivery, including intensity-modulated RT (IMRT), stereotactic RT (stereotactic radiosurgery [SRS] and stereotactic body RT [SBRT]), image-guided (eg, magnetic resonance imaging [MRI]-guided or computed tomography [CT]-guided) brachytherapy, and particle therapy (eg, protons), allow clinicians to spare organs better while selectively targeting tumor-containing regions. Optimal patient positioning and organ/tumor motion management are also critical to maximize the therapeutic ratio of high-precision RT. Toxicity, nonetheless, is common and results from higher RT doses, along with combined effects of other cancer treatments and baseline organ dysfunction. General approaches to some of the more common RT effects are briefly reviewed in Table 1.

Pathophysiology of Radiation Injury

Mechanisms of radiation injury are summarized in Figure 1. In brief, ionizing radiation directly or indirectly (via reactive oxygen species) damages DNA, prompting a cascade of events that may lead to cell death. The degree of cell killing and resistance varies based on properties such as degree of differentiation and mitotic rate, and also cumulative and fractional radiation dose.[7]

RT side effects are categorized as acute, subacute, or late. Acute effects begin within 1 or 2 weeks after starting RT and often are inflammatory or reflect the depopulation of rapidly growing epithelial cells. Timing of symptoms relates to turnover and transit time for normal tissue stem cells to repopulate damaged tissue; patients finishing RT are counseled that acute side effects may continue to worsen before recovery. Late effects often reflect fibrosis, vascular injury, or other gradual changes in slowly dividing tissues, with end-organ damage possibly manifesting years after treatment. Residual DNA damage may rarely cause delayed carcinogenesis.

Because RT is a locoregional treatment, anatomic properties of affected organs and tissues influence the pathogenesis and clinical presentation of toxicity. Organs can be considered to consist of functional units arranged either in parallel (eg, liver and lung) or in series (eg, esophagus and nerve), each with characteristic pathways to toxicity (Fig. 2).[3]

Skin, Connective Tissues, and Breast

Radiation Dermatitis

Skin, bone, and soft tissue receive significant radiation exposure in most treatment settings. Major late cutaneous toxicity is infrequent because of the physical properties of high-energy x-rays that preferentially spare superficial tissues. Radiation dermatitis (akin to a temporary sunburn), however, is common and expected in the treatment of head and neck, vulvar, anal, skin, extremity (eg, sarcoma), and breast cancers. Effects are caused by cutaneous epithelial depopulation, with symptoms ranging from self-limited erythema to painful moist desquamation. Much of the literature is derived from breast cancer (in which RT is used with lumpectomy for breast conservation or for high-risk features after mastectomy).[8] Risk is highest in the postmastectomy setting (approximately 20%-40% grade 2-3 moist desquamation), in which skin is intended to receive a higher dose, and in large-breasted women. Skin folds (eg, inframammary fold, groins, perineum) are particularly susceptible. Management is similar in all clinical situations, with general skin care including cleansing and avoidance of irritation. Steroid creams (eg, mometasone) were found in a randomized trial to decrease moist desquamation by approximately one-third.[9] Adhesive silicone dressings and silver sulfadiazine are also effective in decreasing and managing moist desquamation, with a low threshold to supplement with topical antifungals because concurrent yeast infection is common.[10,11] Opiate pain medications should be prescribed in moderate-to-severe cases, as symptoms may worsen for 1 or 2 weeks after RT before quickly improving.

Soft Tissue Fibrosis and Breast Cosmesis

In clinical situations similar to radiation dermatitis, subcutaneous soft tissue can develop late fibrosis from high-dose RT, akin to wound healing after surgery and exacerbated by treatment with any combination of surgery, RT, and/or chemotherapy.[12] Although usually subclinical, tissue hardening may produce pain and limitation of motion. Effects are caused by inflammation and acute injury, leading to fibroblast proliferation and increased extracellular matrix deposition, along with vascular insufficiency.

Fibrosis may adversely affect breast cosmesis, although >80% to 85% of women receiving breast conservation (lumpectomy and RT) report good or excellent cosmetic results.[13] Patients who require RT after mastectomy with reconstruction are at higher risk of suboptimal cosmesis. Outcomes vary based on reconstruction type and timing (immediate at surgery or delayed after RT), although evidence is conflicting.[14,15] With implant-based reconstruction, fibrosis may lead to capsular contracture and implant failure in 15% to 30% of patients.[16] With autologous graft reconstruction, both fibrosis and vascular insufficiency may

TABLE 1. Common Management Considerations[a]

Toxicity	Timing	Management
Skin, connective tissues, and breast		
Dermatitis	Acute	• Dry and avoid irritation; steroid creams (for high risk: mometasone 0.1% bid from RT start), aloe, corn starch, nystatin powder; adhesive silicone, silver sulfadiazine, opiates for severe moist desquamation
Fibrosis	Late	• Pentoxifylline (400 mg bid-tid) and vitamin E (400 IU qd) for 6 mo starting 2-4 wk after RT (eg, for RT after postmastectomy reconstruction)
Lymphedema	Late	• Physical therapy (manual lymphatic drainage), compression devices/garments, complete decongestive therapy
Bone pain flare	Acute	• Dexamethasone 2-8 mg qd for 3-5 d at/before RT or prn for painful bone metastases, depending on expected/observed severity
CNS		
CNS edema/radiation necrosis	Both	• Dexamethasone 2-16 mg qd for ≥1-4 wk based on severity, with GI prophylaxis and steroid taper for longer courses; bevacizumab/surgery for refractory necrosis
Cognitive	Late	• Before RT: Memantine 5-10 mg qd, increasing to 20 mg by 4 wk, total 24 wk; after RT: donepezil 5 mg qd for 6 wk, 10 mg qd for 18 wk
Head and neck		
Mucositis	Acute	• Salt and baking soda/hydrogen peroxide rinse or other mouthwash containing lidocaine, diphenhydramine, antacid, and/or nystatin; opiates if severe and affecting nutrition, with long-acting (transdermal preferred) and breakthrough
Xerostomia	Both	• Xylitol-containing candies/gums, saliva substitutes, and mouthwashes
Dentition/osteoradionecrosis	Late	• Fluoride trays for routine care; pentoxifylline and vitamin E +/− clodronate, antibiotics, and prednisone for conservative management of osteoradionecrosis
Fibrosis (dysphagia, jaw, neck)	Late	• Speech/language pathologist for dysphagia, jaw physical therapy for trismus, massage therapy for neck stiffness/lymphedema, acupuncture for pain
Lung		
Pneumonitis	Late	• Prednisone 40-60 mg qd for 2-4 wk, tapering over 4-8 wk total, depending on severity and comorbidities, with GI prophylaxis
Heart		
Pericarditis	Acute	• NSAIDs, eg, ibuprofen 200-800 mg tid prn for 1-2 wk
Gastrointestinal		
Esophagitis	Acute	• Soft/liquid diet; antacids, viscous lidocaine (before swallowing), and/or opiates (before meals); fluconazole for empiric treatment of candida esophagitis
Nausea	Acute	• Antacids, prn ondansetron or prochlorperazine (both tid and alternating if severe)
Gastritis/ulceration	Both	• Avoid gastric irritants; antacids and prolonged course of proton pump inhibitors; formalin for refractory bleeding, coagulation if severe
Enteritis	Both	• Low fiber/residue/fat diet; loperamide (qd/bid prn) and/or diphenoxylate/atropine; subcutaneous octreotide (100 μg tid for 3-5 d) if refractory with dehydration
Proctitis	Both	• Steroid creams; for late hematochezia, sucralfate enema, formalin, and coagulation
Genitourinary		
Obstructive urinary symptoms	Both	• Avoid fluids before sleep, minimize caffeine and alcohol; α-blockers (eg initiate/increase tamsulosin dose for 3-6 mo after RT); steroids if severe
Cystitis	Both	• Rule out urinary tract infection; phenazopyridine for dysuria; antimuscarinics (eg, oxybutynin, solifenacin) for severe frequency, urge incontinence, and/or bladder spasms
Sexual		
Female	Late	• Topical estrogens, regular vaginal dilator usage, pelvic floor physical therapy
Male	Late	• Phosphodiesterase inhibitors (eg, sildenafil), vacuum devices, urologic interventions

Abbreviations: +/−, with or without; bid, twice daily; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; prn, as needed; qd, once daily; RT, radiation therapy; tid, 3 times daily.
[a]Note: This table describes general approaches to select commonly-encountered RT effects; treatment of actual patients should always be individualized.

lead to impaired wound healing, infection, fat necrosis, and graft failure.[17] A 6-month course of pentoxifylline and vitamin E (a combination that decreases blood viscosity and inflammation) may be prescribed after RT to lower the risk of fibrosis and improve tissue healing/compliance after RT.[18,19]

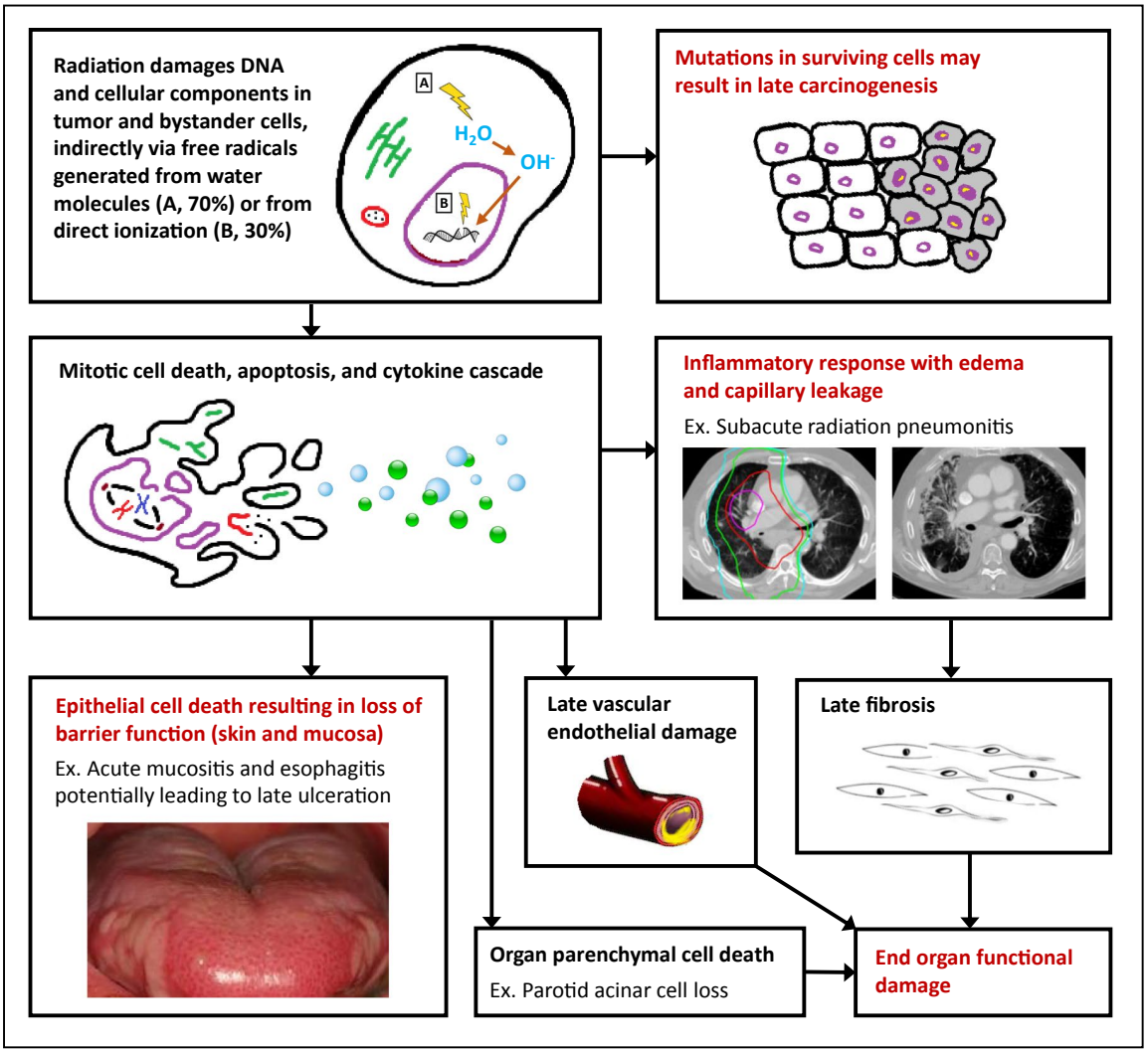

FIGURE 1. Pathophysiology of Radiation Effects on Normal Tissue. Ionizing radiation initiates its effects by damaging DNA, prompting a cascade of events potentially leading to toxicity (clinical manifestations of toxicity are indicated with red text). Acute effects are usually inflammatory or reflect epithelial depopulation/repopulation. Late effects often reflect fibrosis, vascular injury, or gradual parenchymal injury, which may decrease global organ function.

Lymphedema

Lymphedema can be a management problem for any peripheral tumor site requiring nodal management (eg, axilla for breast cancer, groin for vulvar cancer, and both axilla and groin for extremity melanoma) and occurs because of impaired lymphatic drainage from fibrosis and/or direct nodal removal. Symptoms include swelling, pain, and limited range of motion, which may develop immediately or in months to years.

Lymphedema has been best studied in breast cancer, in which evaluation of the axilla is necessary for most patients planned for curative treatment. Severity and risk relate to the degree of surgery (sentinel lymph node biopsy vs axillary lymph node dissection) and radiation (breast-only RT vs nodal RT). Risk ranges from 5% after sentinel lymph node sampling with or without RT to approximately 20% to 30% after full axillary lymph node dissection followed by comprehensive regional nodal RT.[20,21] Because lymphedema may be irreversible, early detection is important to prevent or delay symptoms. Physical therapy (including manual lymphatic drainage) and compression are the initial management. Complete decongestive therapy is most effective but is a rigorous regimen incorporating manual drainage, compression, skin care, and exercises. Novel surgical techniques involving lymphatic bypass and lymph node transfer have been investigated with promising results.[22]

Bone

Acute effects on bone include hematologic suppression (discussed separately) and inflammation. Palliative RT for bone metastases may cause an acute "pain flare," which reflects the release of inflammatory cytokines and tumor response rather than direct RT effects. Steroids are effective for both prophylaxis of RT-associated pain flare and treatment of baseline tumor-associated bone pain. A phase 3 trial showed that pain flare occurred in 26% versus 35% of patients receiving

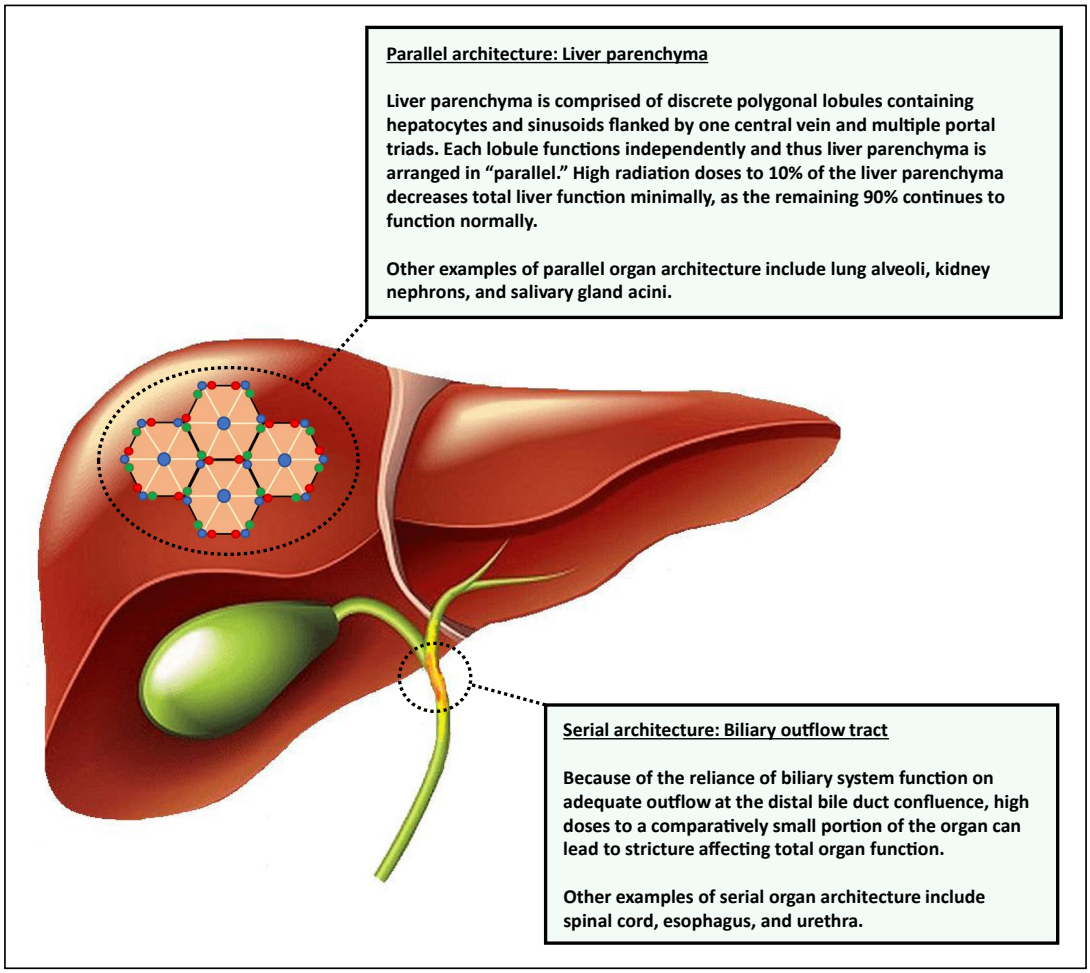

FIGURE 2. Parallel Versus Serial Organ Architecture, the Liver as a Model. Parallel organs are sensitive to the percentage volume receiving radiation (and thus the amount of functioning parenchyma remaining) but can tolerate high doses to small areas. The reverse is generally true for serial organs in which damage to one segment can affect total organ function.

dexamethasone versus placebo, but steroids occasionally caused hyperglycemia.[23]

Late skeletal effects of RT are most pertinent in children, who may develop deformities because of impaired/asymmetric bone growth.[24] Demineralization and osteoporosis may increase the risk of symptomatic fracture, especially of the ribs, femur, and pelvis, although most heal with conservative management. Pelvic insufficiency fractures are more common in females, the elderly, and others with low body mass index or bone density. A population analysis found a 2% to 8% absolute increase in 5-year pelvic fracture risk in patients with pelvic malignancies who received versus did not receive pelvic RT.[25,26] Vertebral body fractures may occur weeks to months after RT for spine metastases (with a slightly higher, 10%-15% risk at 3-12 months with SBRT, which however has the advantage of better tumor control). These tend to be subacute rather than late, with a major contribution from destabilization from tumor cell death, although the risk from tumor progression outweighs that attributed to RT.[27]

Central Nervous System

Acute Effects

RT is frequently used in the treatment of neoplasms in or near the brain and spinal cord, including benign brain tumors, malignant gliomas, ocular/CNS lymphoma, and metastases. SRS is preferred for brain metastases (except when extensive), but whole-brain RT (WBRT) is routinely used for certain settings and histologies (eg, hematologic malignancies and small cell lung cancer) and where SRS capabilities are unavailable. Acute toxicity most often includes fatigue, which is poorly understood but experienced in all RT settings and increases with treatment volume.[28] Patients receiving WBRT can also develop mild-to-moderate acute dry mouth and dry eye from dose to the parotid and lacrimal gland, respectively.[29,30] Patients receiving cranial RT occasionally experience headache, nausea/vomiting, and other signs of increased intracranial pressure from generalized edema. Treatment of these and many other acute/subacute inflammatory radiation side effects often involves use of

dexamethasone. Surgical decompression is used for extreme situations. Depending on the primary pathology, patients may have mild-to-severe focal neurologic deficits and, rarely, neurologic events like stroke and seizure (data are lacking, but likely <1%).

Neurocognitive

Neurocognitive changes are a well known potential late effect of CNS irradiation and manifests from months to years after treatment, depending on RT dose and volume of irradiated brain. In pediatric patients, cranial RT to developing brain tissue is associated with worse IQ and psychological health.[31] In adults, neurocognitive RT effects have been best studied after WBRT, although assessment may be confounded by age, treatment, and disease-related factors. Effects are at least partly because of direct suppression of neuronal stem cells in the hippocampus, an organ implicated in memory formation and whose dysfunction is associated with Alzheimer disease.[32] Delayed microvascular changes from vascular endothelial damage may also lead to symptoms mimicking vascular dementia.[33] Treatments for those neurologic diagnoses, including memantine and donepezil, may mitigate the neurocognitive effects of cranial RT.[34,35] Recently, hippocampal-sparing WBRT was found to improve both objectively scored and patient-reported neurocognitive outcomes in a large randomized controlled trial, establishing the hippocampus as an "avoidance structure" for cranial RT.[36] Patients who require CNS RT and intrathecal chemotherapy/high-dose methotrexate (eg, for CNS lymphoma) may experience severe, progressive leukoencelopathy,[37,38] although risks appear to be minimal with the lower WBRT doses used in most current practice (there was no significant neurotoxicity in one phase 2 trial with 6 years of follow-up).[39]

Radiation Necrosis

The increasing use of SRS to deliver high-dose, focal RT (while sparing sensitive cranial functional areas and preserving quality of life) has led to increasing recognition of radiation necrosis, which may present months to years after treatment. For patients receiving SRS for metastases, rates of radiation necrosis range from 5% to 20%, depending on factors that include dose and tumor size.[40] The etiology is complex, with contributions from CNS edema/inflammation leading to increased intracranial pressure, glial cell injury with neuronal demyelination, and vascular endothelial damage with resultant hypoxia leading to overexpression of vascular-endothelial growth factor (VEGF) and abnormal angiogenesis of small, leaky vessels.[40,41]

Patients who develop radiation necrosis may be asymptomatic, with mild radiographic edema, or they may have severe neurologic symptoms with enlarging, ring-like contrast enhancement mimicking tumor progression. Steroids are the treatment of choice for symptomatic patients, with bevacizumab (a VEGF inhibitor) showing some efficacy in patients who are refractory to steroids.[42,43] Patients may require surgery, which may be preferred if underlying tumor progression is suspected. Recent evidence suggests that immunotherapy may increase the risk of radiation necrosis.[44,45] Fractionated SRS (3-5 treatments as opposed to a single treatment) may reduce the risk in this and other high-risk scenarios, as higher radiation dose per fraction tends to produce more late effects.[46,47]

Endocrine

Radiation for pituitary adenomas and other skull base tumors, including craniopharyngioma, chondrosarcoma, chordoma, and nasopharyngeal carcinoma, may result in endocrinopathies via effects on the hypothalamic-pituitary axis and may be cumulative with toxicities from surgery or tumor. Effects on the pituitary gland are dose-dependent and age-dependent; growth hormone, prolactin, and thyroid deficiencies appear at doses <30 Gy, with gonadal hormone effects also prominent in children that may affect fertility and onset of puberty.[48,49] At higher doses (eg, >50 Gy), ACTH may be affected, along with more pronounced deficits in the remaining hormones. Up to 50% of patients receiving pituitary-directed radiation may develop endocrinopathies of varying clinical significance, and thus endocrinology consultation is recommended for management.[50]

Other

Hair loss from follicle stem cell depletion occurs to various degrees in most settings involving cranial RT (especially with WBRT), and the risk of permanent or severe hair loss increases with doses >40 Gy.[51] The risk of cataracts is 20% with lens doses of 7 Gy and is >70% with doses >20 Gy.[52] There is an age-dependent risk of cerebrovascular disease through late vascular injury, particularly to vessels within the circle of Willis.[53]

The most severe late toxicities of CNS RT are rare and include complications from high dose to the brainstem,[54] radiation myelopathy from high dose to the spinal cord,[55] and vision loss from damage to the optic nerve or chiasm.[56] Effects are caused predominantly by white-matter damage from glial and vascular injury.[57] A rich RT literature exists that has established dose limits for these critical organs; doses below these limits have a very low probability of producing these injuries. For instance, based on several seminal monkey experiments, the spinal cord was shown to be more sensitive to total dose (myelopathy increased at doses >60 Gy) than volume (length) of exposed cord. Tolerance for further irradiation increases over time; the spinal cord can tolerate around 50% more dose a year or more after initial RT.[58,59] Clinical experiences in humans have been consistent with these estimates. To minimize the risk of a particularly severe toxicity

to negligible (eg, almost 0%) levels, the universal dose limit for the spinal cord (and, similarly, for the brainstem and optic tracts) has been established at approximately 50 Gy given with conventional dose-fractionation schedules.[55]

Head and Neck

Acute Effects

RT is often used as a primary treatment or with surgery and chemotherapy for head and neck cancers (HNCs) (oral cavity, paranasal sinuses, nasopharynx, oropharynx, and larynx). IMRT is standard of care for HNC, with its ability to spare sensitive anatomy. Patients receiving RT for HNC often experience moderate-to-severe acute mucosal toxicity (correlating with treatment volume and dose) requiring aggressive supportive management. Mucosal epithelial damage leads to progressive, painful mucositis, which is more severe with concurrent platinum-based chemotherapy (which increases the relative risk of grade 3 mucositis by ≥50% in randomized trials).[60] Pain management with liquid or transdermal narcotic medications is usually required. A gargle of salt and baking soda or hydrogen peroxide can be useful. Commonly used oral formulations (eg, magic mouthwash, BMX mouthwash, etc) incorporate a combination of lidocaine, diphenhydramine, antacid, and/or nystatin.[61] Palifermin (keratinocyte growth factor)[62,63] and doxepin (a tricyclic antidepressant)[61,64] also reduce mucositis severity but are not routinely used. Nutritional status is critical and feeding tubes are sometimes needed; these should be planned in advance of fulminant symptoms to minimize treatment breaks. Other common acute toxicities include nausea and dry mouth with bothersome, thick saliva. Patients may develop loss of taste (dysgeusia) early in treatment because of decreased saliva, blockage of taste receptor pores, and direct damage to taste receptor cells. Small studies suggest that zinc supplementation has a mild protective effect.[65]

Xerostomia

Xerostomia (dry mouth) is a significant toxicity of head and neck RT that begins during therapy and may improve for up to 1 or 2 years. Xerostomia occurs because of RT-induced apoptosis of acinar cells in the parotid and submandibular glands, with some contribution from minor salivary gland damage. Salivary recovery ranges from complete to minimal and depends on the volume of these organs receiving threshold doses (20-30 Gy for parotid, 30-40 Gy for submandibular glands).[66] Patients who require bilateral neck RT are at highest risk. Amifostine (a selective radioprotector) may reduce xerostomia when given during radiation, but its use is challenging because of the requirement for daily intravenous infusion and toxicities, including nausea, vomiting, and hypotension.[67] Treatments for xerostomia have limited efficacy. Patients are counseled to use saliva-stimulating candies/gum (containing xylitol), saliva substitutes, and mouthwashes (eg, Biotene) and to carry beverages. Muscarinic cholinergic agonists improve salivary flow but may cause toxicity.[68,69] With modern techniques, it is usually possible to lessen the dose to the salivary glands so that long-term symptoms are mild or moderate.[70]

Dysphagia

In combination with surgery, chemotherapy, and local tumor destruction, RT may lead to dysphagia and aspiration from damage to the larynx and muscles involved in swallowing (including tongue, pharyngeal constrictors, and epiglottis). Effects are worsened by xerostomia, neck fibrosis, and, rarely, cranial neuropathies (eg, hypoglossal nerve palsy). Some patients need a permanent feeding tube, either from persistent acute dysphagia that fails to recover or from late toxicity. Studies suggest improved outcomes with the use of swallowing exercises; speech language pathologists are critical in management and determining dietary and feeding tube needs.[71] Fortunately, severe late dysphagia is less common in patients treated with modern conformal techniques with minimization of radiation dose to the pharyngeal constrictors and larynx.[72] Furthermore, treatment de-intensification efforts are changing standard of care for human papillomavirus-associated oropharynx cancer (now the most common variant, and very sensitive to both radiation and chemotherapy) using reduced radiation and chemotherapy intensities to minimize mucositis, xerostomia, and dysphagia while retaining >90% locoregional control rates in prospective trials.[73,74]

Dentition

Patients receiving RT for HNC are at risk for dental caries from decreased saliva production and direct demineralization of the enamel and dentine-enamel junction. Pre-RT and post-RT dental evaluations, along with interventions including topical fluoride, are recommended. Uncommonly, hypoxia from decreased blood flow can lead to osteoradionecrosis (approximately 5% risk in the modern era) with exposed and necrotic bone, usually the mandible. Risk factors for osteoradionecrosis include poor baseline oral hygiene, areas of bone receiving high (>60 Gy) dose, and either pre-RT or post-RT dental extractions; it is therefore generally advised to extract only nonrestorable teeth.[75] Hyperbaric oxygen has been investigated in both the prophylactic and treatment settings with mixed results[76-78] and is recommended only in refractory cases of osteoradionecrosis. One phase 2 trial showed promising efficacy using prolonged pentoxifylline, vitamin E, clodronate, antibiotics, and prednisone with devitalized tissue removal. Of 54 patients with refractory osteoradionecrosis, 62% and 92% had healing by 4 and 12 months, respectively.[79] Most patients improve with conservative management.[80]

Ototoxicity

Cisplatin (with known ototoxicity) is commonly used in the treatment of HNC and, in combination with radiation

effects on the middle and inner ear, may lead to hearing loss and tinnitus.[81] RT-associated sensorineural hearing loss may worsen over months to years after treatment. The risk increases with RT dose to the cochlea (>30% risk of some degree of hearing loss at doses >45 Gy) because of a combination of vascular insufficiency, neuronal demyelination, and loss of hair cells. Conductive hearing loss may result from damage to middle ear structures (such as the tympanic membrane) or effusion resulting from eustachian tube dysfunction, which is more likely to be reversible. Vestibular deficits, including vertigo and imbalance, may also occur.[82]

Other

Hypothyroidism is common in patients receiving RT for HNC because of exposure of the thyroid gland, and screening is recommended starting 6 months after RT. Neck RT can lead to increased atherosclerosis of the carotid arteries and slightly increases the risk of stroke in the decades after treatment. Screening ultrasound has been recommended by some starting 3 to 5 years post-RT, as carotid intima thickness may increase by 20% to 40% when receiving high doses.[83] Patients receiving RT for sinonasal and nasopharynx cancer are at risk for CNS toxicities, as discussed above. Radiation in combination with neck dissection may lead to neck fibrosis, producing shoulder and neck stiffness, lymphedema, and trismus.[84] In severe cases, fibrosis and direct damage to nerves (often in areas with gross disease that receive more intensive treatment) may produce brachial plexopathy,[85] which may also occur with apical lung tumors and, rarely, with breast cancer treatment (<2% absent tumor-related factors).[86] Physical therapy incorporating jaw exercises and massage/manual drainage are important and are incorporated early in post-RT follow-up. Acupuncture may reduce pain in these settings.[87]

Lung

RT-induced lung injury is important to consider with treatment for lung and esophageal cancer and other thoracic malignancies, including (to a lesser degree) breast cancer. Lung injury usually manifests as subacute radiation pneumonitis or progressive, late fibrosis, and clinical severity correlates with volume of the irradiated lung. Effects are caused by endothelial damage and congestion of delicate alveoli, impairing gas exchange, along with an exudative, inflammatory cascade of cytokine-mediated fibroblast proliferation and fibrosis. In the subacute setting, the degree of the inflammatory response is thought to be responsible for radiation pneumonitis, with risk correlated with TGF-β and IL-6 levels.[88,89] Various RT metrics have been used to predict the risk of lung injury, including the mean lung dose and the percentage of lung receiving >20 Gy.[90]

Radiation pneumonitis usually presents several months after treatment and ranges from CT findings (concentric, consolidative, and ground-glass changes, usually within irradiation fields), either alone or with cough and shortness of breath, to severe pneumonitis requiring supplemental oxygen (grade 3) or hospitalization. Pneumonitis may independently be caused by chemotherapy (especially taxanes) and immunotherapy.[91,92] In a pivotal randomized trial establishing immunotherapy's benefit in stage III non-small cell lung cancer, 34% versus 25% of patients receiving immunotherapy versus placebo after chemoradiation developed some degree of pneumonitis, but the risk of grade ≥3 pneumonitis was low, approximately 3%, for both study arms.[93] Given that cardiopulmonary comorbidities are common in patients with lung and esophageal cancer, it is critical to identify treatment-related pneumonitis as it is often reversible. Treatment is directed at suppressing the inflammatory response with high-dose steroids (40-60 mg prednisone tapering over 4-8 weeks).

In contrast to the relatively early presentation of radiation pneumonitis, alveolar fibrosis progresses over several years. Symptoms are related to the amount of residual functional lung tissue. Most patients who receive high-dose RT to the lung will have radiographic evidence of fibrosis and sometimes perfusion abnormalities on single-photon emission CT.[94] Patients may have a decline in pulmonary function tests, although they often are asymptomatic without need for intervention. Similar to other settings, pentoxifylline and vitamin E decrease radiographic lung fibrosis, although the clinical significance is unclear.[95] Pre-existing interstitial lung disease may increase the risk of pulmonary toxicity from RT 5-fold to 10-fold.[96]

High doses of RT to the proximal bronchial tree may very rarely produce severe bronchial or vascular injury, often enhanced by local tumor destruction. These include hemorrhage, bronchial stenosis, and fistula and require urgent intervention. Although rare with conventionally fractionated chemoradiation, fatal central toxicities have been reported in trials exploring SBRT for tumors abutting/invading carina, mainstem bronchi, and/or esophagus; less aggressive (eg, moderate) fractionation may be prudent in those clinical scenarios.[97,98]

Heart

The most recognized RT-associated cardiotoxicity is an increased risk of ischemic heart disease and myocardial infarction years to decades after treatment, attributed to decreased perfusion from accelerated coronary atherosclerosis along with microvascular damage.[99] Most studies are in long-term survivors of mediastinal lymphoma or left-sided breast cancer treated with older techniques and, for lymphoma, higher doses and much larger volumes than are used now. Cardiac risk is also elevated in patients receiving trastuzumab and anthracyclines, which are often used for these malignancies and which may cause cardiomyopathy independent of RT. In one study of Hodgkin lymphoma survivors treated between 1965 and 1995, the 20-year cumulative incidence of cardiovascular disease was approximately 22% with both

mediastinal RT and anthracyclines, 15% with either mediastinal radiation *or* anthracyclines, and 7% with neither.[100]

Although "tangential" irradiation fields are used to minimize cardiopulmonary exposure when delivering left breast RT, the left anterior descending artery and left ventricle may receive incidental dose, and this dose directly correlates with cardiac risk.[101] Cardiac perfusion deficits on single-photon emission CT may appear as early as 6 months after RT and correlate with volume of irradiated left ventricle.[102] There is now widespread recognition of this issue and common adoption of techniques including deep-inspiratory breath hold, which separates the breast and heart. Together with acceptance of partial breast treatment for early stage disease, these techniques allow for excellent cardiac sparing. Perfusion deficits appear decreased with the breath hold technique, likely reflecting a minimal cardiac risk.[103]

Larger heart volumes than in breast cancer may be irradiated to high doses with treatment of mediastinal lymphomas, lung cancer, and esophageal cancer. In addition to ischemia, patients may experience pericardial and valvular disease, arrhythmias, and cardiomyopathy.[104,105] Acute inflammatory pericarditis may occasionally occur, although asymptomatic pericardial effusions are more common (exceeding 15%-20% in patients with lung cancer undergoing chemoradiation).[106,107] Only a minority require interventions such as pericardiocentesis or pericardial window. Rarely, pericardial collagen deposition can lead to a severe, constrictive pericarditis. Fibrotic changes may also explain late valvular dysfunction and restrictive (diastolic-predominant) cardiomyopathy, although heart failure itself may occur independently or secondarily because of other cardiac effects. Finally, RT may lead to increased risk of arrhythmia through effects on conduction pathways, but the pathophysiology is poorly understood and easily subject to confounding from intercurrent illness.

In young patients with Hodgkin lymphoma receiving mediastinal RT (before contemporary chemotherapy-based treatment with decreased RT doses/field size), the risk of late cardiac disease of various types increased over time and was estimated to be 20% to 30% several decades after treatment.[104] In contrast, patients with lung cancer and esophageal cancer (who are more likely to have baseline cardiopulmonary comorbidities) may present with earlier cardiac events.[106] IMRT and particle therapy may reduce the combined cardiopulmonary dose and likely improves the therapeutic ratio.[108] Cardio-oncology is an evolving specialty that seeks to both risk-stratify patients before potentially cardiotoxic treatments and optimize follow-up heart care.[109]

Gastrointestinal

Esophagus

Acute esophagitis is a common toxicity of RT after treatment of lung and esophageal cancer and, occasionally, with palliation of upper thoracic vertebral bone metastases. Epithelial depopulation and inflammation lead to symptoms beginning several weeks into treatment, with severity dependent on both total radiation dose and length of esophagus receiving high doses.[110] Ensuring adequate nutrition is critical and involves counseling on soft/liquid diets, analgesics, antacids, and solutions containing viscous lidocaine. Feeding tubes are usually not required. It is important to rule out the possibility of candida esophagitis (a fairly common occurrence in patients with cancer), which can mimic radiation esophagitis, with a low threshold for empiric treatment. In the definitive treatment of lung cancer, IMRT may minimize esophageal dose and reduce the incidence and severity of esophagitis (Fig. 3).[111]

Although acute symptoms improve 7 to 10 days after RT, severe esophagitis can cause scarring and late esophageal stricture.[112] Many patients receiving chemoradiotherapy for esophageal cancer also undergo esophagectomy, which may independently produce a stricture. Management consists of dietary counseling/therapy and dilation, which often needs to be repeated. Other, rarer but potentially serious late complications of esophageal cancer treatment include esophageal dysmotility because of neuronal injury and tracheoesophageal fistula (usually related to unsuccessful healing of baseline tumor invasion into airway). In one prospective study of 212 patients with unresectable, locoregionally advanced disease receiving 60 Gy chemoradiation, fistula occurred in 25% of patients with T4 disease invading adjacent structures, versus 8% in patients with T2-T3 disease.[113]

Liver

High-dose, focal RT is used for hepatocellular carcinoma, liver metastases, and cholangiocarcinoma, with toxicity determined by the volume of viable hepatic parenchyma remaining after RT (Fig. 2).[114] Focal RT is usually very well tolerated, with no clinically significant effects in most patients who have adequate baseline liver function. However, in borderline patients, RT may lead within weeks or months to a general decline in hepatic function, worsening Child-Pugh score, increasing ascites, and, in the worst cases, encephalopathy and death. Patients with preexisting severe cirrhosis (as seen with hepatocellular carcinoma) and larger treatment volumes are at higher risk. RT is particularly advantageous for solitary central tumors abutting biliary/vascular structures that complicate surgical or percutaneous management. Severe toxicity is minimized through careful patient selection (usually Child-Pugh A and select B) and treatment planning (SBRT, IMRT, or protons to ensure adequate sparing, eg, ≥700 cc, of functional liver).[115] Hepatobiliary outflow tract damage is infrequently a clinical problem but can result in biliary obstruction (Fig. 2).[116] Although rarely used, whole liver doses >30 to 35 Gy may cause anicteric hepatomegaly and elevated hepatic enzymes, particularly alkaline phosphatase.[117,118] This is thought to represent a veno-occlusive

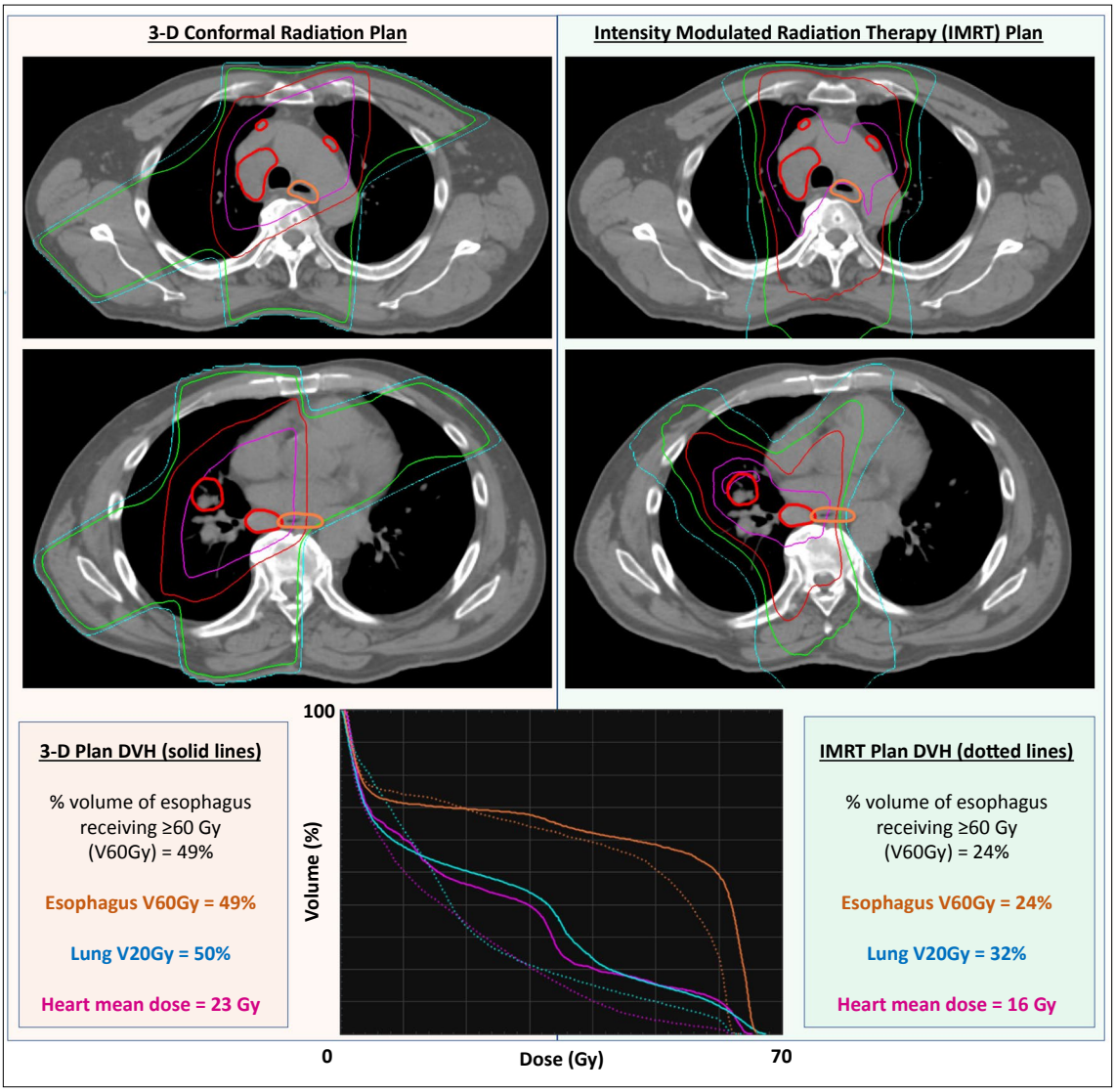

FIGURE 3. Advantages of Modern Radiation Techniques. Three-dimensional (3-D) (left) and IMRT (right) radiation plans for a patient with stage III non-small cell lung cancer prescribed 60 grays (Gy). Thin blue, green, red, and purple lines represent 20 Gy, 30 Gy, 40 Gy, and 60 Gy, respectively. Bold red and orange lines represent gross tumor and esophagus, respectively. Dose volume histograms (DVHs) are shown below for 3-D (solid lines) and IMRT (dotted lines) plans. IMRT brings doses within tolerance levels for the esophagus, lungs, and heart.

disease leading to portal hypertension and can occur months after completion of RT.

Stomach and Small Bowel

RT is commonly used for upper abdominal tumors (eg, pancreas, stomach, and gastroesophageal junction), often with chemotherapy and/or surgery. Patients receiving palliative RT may also experience toxicity from incidental irradiation of abdominal organs.[112] Gastric and duodenal epithelial depopulation and inflammation may acutely or subacutely produce symptoms ranging from mild gastritis to painful ulceration, which is worsened by baseline acid disease. Management is similar as for acid reflux and peptic ulcer disease: antacids, proton pump inhibitors, and avoidance of irritants.[112] Ulceration and bleeding can develop years after RT, but the risk is approximately 5% with doses <50 Gy. These may be managed with formalin, coagulation, or embolization if conservative measures fail.[119]

Radiation-associated nausea is thought to be specific to stomach exposure. In contrast to epithelial effects (which increase gradually over weeks), nausea and/or vomiting attributed to RT often occur in the first few hours or days and may lessen thereafter. The etiology is thought to be release of factors, including 5-hydroxytryptamine-3, serotonin, neurokinin-1, and dopamine, that act on central receptors.[120] These symptoms can usually be alleviated by antiemetics or a brief radiation break. The risk of severe symptoms is lower with smaller treatment volumes and lower daily radiation doses.

In both small and large bowel, epithelial depletion, inflammation, and crypt abscess formation may lead to

symptoms collectively termed "radiation enteritis." Acute effects begin several weeks into therapy and range from mild bowel frequency/urgency to severe, watery diarrhea requiring intravenous hydration. Symptoms are worsened by concurrent chemotherapy (especially fluorinated pyrimidines such as 5-fluorouracil and capecitabine). Patients with active inflammatory bowel disease may be at higher risk. Patients are counseled to avoid dietary fibers, including foods with skins, seeds, and leafy greens, that may worsen symptoms. Antidiarrheals (eg, loperamide or diphenoxylate/atropine) are often used, with subcutaneous octreotide effective in severe cases through its antisecretory effects.[121]

With larger treatment volumes and higher doses, late radiation enteritis can ensue through a combination of obliterative arteritis and fibrotic changes (including sequelae of ulcer healing), resulting in malabsorption, bleeding, and impaired gastrointestinal motility. Late small bowel obstruction may also occur in patients receiving abdominopelvic surgery with or without radiation; the risk was 11% in the Stockholm III trial of preoperative RT and surgery for rectal cancer.[122] Thus bowel is a critical "organ at risk" prioritized for avoidance during RT planning. For pelvic malignancies, treatment with the bladder full is often used to displace bowel away from irradiation fields.

Patients receiving abdominal RT may develop nutritional deficiencies, although the extent to which RT contributes is unclear. Gastric surgery and RT may lead to deficiencies in iron, calcium, and intrinsic factor (and, subsequently, vitamin B12).[123] Effects on the duodenum and small intestine may cause bile salt malabsorption and diarrhea, which may respond to cholestyramine.[124] Patients receiving large-volume pancreatic irradiation may require digestive enzyme replacement and be at mildly increased risk for diabetes because of endocrine (insulin and C-peptide) and exocrine (lipase and α-amylase) deficiencies.[125,126]

Finally, ^{177}Lu-Dotatate (peptide receptor radionuclide therapy, an example of theranostics) was recently approved for somatostatin receptor-positive neuroendocrine tumors of the gut. The systemic delivery of ^{177}Lu-Dotatate complicates dosimetric assessments of toxicity, but the principal toxicities in a phase 3 trial were gastrointestinal effects (consistent with local effects of RT near tumor targets). However, fatigue, alopecia, and low-grade cytopenias were also observed, possibly consistent with systemic RT effects.[127]

Colon, Rectum, and Anus

RT is an important treatment for prostate, vulvar, cervical, endometrial, rectal, and anal cancers. Although proximal colon toxicity is rare, anorectal toxicity is important. Symptoms of rectal toxicity (radiation proctitis) include tenesmus, frequency (without high-volume diarrhea), and urgency; chronic symptoms may persist in some patients. Conservative management consists of dietary modification and antidiarrheals. In patients with rectal cancer, symptoms are caused by combined effects of RT, chemotherapy, and surgery (eg, low anterior resection) and are worse with low-lying tumors.[128,129] The anal canal, sphincters, and perianal skin may also receive significant dose in the treatment of low-lying rectal cancers, anal cancer, and vulvar cancer. Acutely, patients may develop cutaneous desquamation requiring supportive management. Late anal toxicities include stenosis and, depending on dose and baseline function, some degree of fecal incontinence from sphincter dysfunction. In one prospective quality-of-life study of 54 patients with anal cancer treated with modern techniques, only 10% had worsened mild or moderate fecal incontinence, whereas 2 patients (with baseline tumor-related incontinence) ultimately required abdominoperineal resection for persistent incontinence.[130]

Patients with cervical cancer and prostate cancer receive high RT doses to focal regions of the rectal wall that predispose to rectal bleeding (hematochezia) years after treatment from mucosal thinning and telangiectasias. Women with bulky cervical cancers receiving chemoradiation with brachytherapy boost may develop rectovaginal fistula, but the risk is lower with modern, image-guided techniques. In the EMBRACE study of 960 patients receiving MRI-guided adaptive brachytherapy after chemoradiation for cervical cancer, the risk of fistula was 12.5% with rectal doses >75 Gy versus only 0% to 2.7% for lower doses.[131] For hematochezia, sucralfate enema is an appropriate initial intervention through its protective effects on mucosa that promote healing.[132] Other treatments include formalin application (which has coagulative properties) and endoscopic interventions, including argon plasma coagulation. It is prudent to proceed conservatively in these situations, as there is a chance of iatrogenic fistula formation with aggressive interventions.[133,134]

Urinary

Urethra

Urethral and bladder toxicity are important considerations for prostate and gynecologic cancers. With prostate RT, high doses to the prostatic urethra are inevitable and commonly produce mild-to-moderate acute obstructive symptoms, including dysuria, nocturia, frequency, urgency, and hematuria.[135] Effects are caused by direct urothelial damage and surrounding prostate inflammation, similar to the presentation of benign prostatic hyperplasia. Symptoms usually respond to medications including α1-receptor antagonists (eg, tamsulosin),[136] and improve over months.

Although toxicities are often worse in patients with baseline obstructive symptoms, RT and androgen-deprivation therapy can sometimes improve late symptoms, presumably by decreasing prostate size.[137] Patients can also develop late obstructive symptoms because of urethral stricture that may

require urologic intervention. Strictures may occur from high-dose RT (generally <5%) or prostatectomy alone but are more common in those who require both (10% with surgery alone and 18% with postoperative RT in one phase 3 trial).[138] Incontinence can also occur, although this is usually postobstructive and is more of a problem after prostatectomy or in patients with a history of transurethral resection of the prostate.[139-141]

Bladder

Bladder toxicity (radiation cystitis) occurs through direct urothelial damage, along with effects on urinary sphincter and detrusor muscle from fibrosis and vascular ischemia.[142] Acute irritative symptoms include frequency, urgency, dysuria, and spasm and may be treated with phenazopyridine and antispasmodics (eg, oxybutynin). Superimposed urinary tract infections should be ruled out. Hemorrhagic cystitis is comparatively rare, occurring years after treatment in <5% of patients treated for cervical and prostate cancers. Management may include cystoscopy with clot evacuation or coagulative intervention.[143]

For muscle-invasive bladder cancer, chemoradiation is an alternative to cystectomy. Patients receiving organ-preserving treatment with chemoradiation may develop chronic low-grade cystitis and decreased bladder compliance. Minimizing the percentage of bladder treated to high dose decreases risk. Most patients have favorable quality-of-life outcomes, and >70% have normal bladder function on urodynamic studies.[144,145]

Kidney and Ureter

Although kidneys are radiosensitive (to doses as low as 10-20 Gy), it is usually possible to minimize toxicity given the parallel structure of the kidney and the ability to spare portions of renal parenchyma from high-dose RT. Radiation nephropathy remains pertinent with total body irradiation for bone marrow transplantation, abdominal pediatric malignancies, including Wilms tumor and neuroblastoma (in which nephrectomy and chemotherapy are often required), and patients with baseline kidney disease.[146] Nephrotoxicity manifests with a subacute decline in renal function occurring within 2 years of RT. Effects are because of capillary endothelial damage leading to progressive glomerulosclerosis and tubulointerstitial fibrosis.[147] Ureteral stricture from RT leading to hydronephrosis is rare but can occur with external-beam RT followed by intraoperative RT during surgery.[142] Proper ureteral shielding and/or avoidance during intraoperative cases is sufficient to minimize risk.

Sexual/Reproductive

Female

In patients of reproductive age, RT and chemotherapy for malignancies within the pelvis may adversely affect fertility, hormones, and sexual development. RT is almost always contraindicated in pregnant women because of the risk of teratogenesis in the developing embryo. Exposure of the ovaries to doses as low as 2 to 5 Gy can decrease fertility and lead to early menopause through accelerated depletion of the fixed oocyte pool and surrounding follicles that produce estrogen and progesterone.[148] Fertility preservation may be achieved through embryo or oocyte cryopreservation. Surgical transposition of the ovaries (oophoropexy) away from the irradiation field (above the iliac crest) may preserve both fertility and hormonal production.[149]

Uterine irradiation decreases adult uterus size and function from vascular insufficiency and fibrotic changes. These effects lead to a reduced probability of pregnancy, a higher risk of pregnancy complications, and low-birthweight babies. Hormone replacement (to promote normal uterine development) and pentoxifylline and vitamin E (to reduce uterine fibrosis) have been investigated, but evidence supporting efficacy is limited.[48,150,151]

Women receiving pelvic RT (including vaginal cuff and cervical brachytherapy) are at risk for sexual dysfunction. Impaired vaginal lubrication along with vaginal stenosis and shortening (because of vaginal epithelial atrophy and fibrosis) can lead to dyspareunia and sexual dissatisfaction.[152,153] Management is usually limited to topical estrogens and frequent vaginal dilator use to maintain vaginal elasticity.[154] In women receiving pelvic RT for anorectal malignancies, treatment with a vaginal dilator in place can help visualize and reduce dose to the anterior vagina, potentially preventing stenosis by reducing the proportion of the vagina that develops RT-associated fibrosis.[155] Referral to pelvic floor physical therapy is essential to optimize quality of life in the survivorship phase of these patients' care.[156]

Male

Spermatogenesis is impaired by very low RT doses, with immature spermatogonia the most radiosensitive, followed by spermatocytes and spermatids. Because of the theoretical risk of embryologic abnormalities from fertilization by genetically compromised sperm, many practitioners recommend against conception during and for up to 1 or 2 years after pelvic RT.[157] Permanent infertility may occur at testicular doses >6 Gy, with lower doses leading to temporary azoospermia lasting months to years.[158] Testicular shielding and cryopreservation of sperm are recommended when fertility preservation is desired. Leydig cells are comparatively radioresistant, with hypotestosteronemia occurring at doses >20 Gy.[49]

Erectile dysfunction may develop after prostate RT because of effects on neurovascular bundles and penile bulb,[159] although assessment is confounded by age-related changes and use of androgen-deprivation therapy. Erectile dysfunction from RT increases over many years after treatment in contrast to impotence from prostatectomy, which may occur

immediately and is usually more severe.[139,140,160] Treatment options include medications, vacuum devices, and penile injections/prostheses.[161]

Hematologic

Hematologic effects of cancer treatment occur principally because of chemotherapy, and the additive effects of focal RT are usually not major. Nonetheless, irradiation of large volumes of blood and bone marrow may contribute to lymphopenia, which has been associated with inferior outcomes after chemoradiation for a variety of cancers.[162,163] However, because of the interplay between competing effects of lymphocyte depletion versus activation (via increased antigen presentation), RT has both immunosuppressive and immunostimulatory properties, a major current research focus given the rapid uptake of both immunotherapy and SBRT.[164] Radiosensitivity of the components of the hematopoietic system varies, with lymphocytes being the most sensitive and circulating platelets the most resistant. Red blood cells are not substantially affected by RT, but bone marrow fibrosis can contribute to chronic anemia.[165] Despite radioresistance of platelets, significant thrombocytopenia may occur after even very low doses of splenic irradiation in patients with extramedullary hematopoiesis.[166]

Carcinogenesis

Cellular effects of ionizing radiation range from cell death to complete DNA damage repair, but sublethal damage with accompanying chromosomal abnormalities or mutations may cause or predispose to cancer. Therapeutic radiation, diagnostic radiology, and nuclear accidents/warheads all have carcinogenic potential.[167,168] Given the long latency to cancer formation, these effects are of greatest clinical significance in younger patients, who also have rapidly proliferating tissues that may be particularly susceptible to secondary tumors. For instance, irradiation of developing breast tissue in the context of increased adolescent hormones may lead to a 5-fold to 15-fold increase in adult and early onset breast cancer.[169] Extensive studies in the pediatric and adolescent populations also show substantial increases in the incidence of cancers of the CNS, salivary glands, soft tissues (eg, sarcoma), thyroid, and skin. Risk may be particularly high in patients with predisposing genetic conditions like neurofibromatosis or Li-Fraumeni syndrome.[170]

Radiation carcinogenesis appears to be a "stochastic" toxicity, with risk increasing with dose and no threshold below which risk is absent. For solid tumors, incidence progressively increases years to decades after exposure, whereas hematologic malignancies arise as early as 2 years, with declining risk after 5 to 10 years.[171] Although quantification of second cancer risk in adults is confounded by the natural increase in cancer risk with age, those arising within irradiation fields are suggestive of RT-associated malignancy. Data from cervical cancer suggest that tissues receiving a moderate dose will have on average a 2-fold relative increase in cancer compared with the general population.[172] Data from prostate cancer show a 1.7-fold increase in late rectal cancer risk.[173] However, the absolute risk increase depends on the baseline cancer incidence, and the survival and/or palliative benefits of RT generally far exceed carcinogenesis risks.

Conclusion

Enormous technological improvements, including CT-guided and MRI-guided planning, IMRT, particle therapy, and better diagnostic imaging, have allowed for major decreases in normal tissue doses and the risk of acute and late toxicity (Fig. 3). Nonetheless, substantial morbidity can result from excessive radiation doses to any organ. Thus treatment-planning atlases, organ dose/tolerance guidelines, and entire journal issues and careers have been dedicated to the understanding of radiation toxicities to help clinicians achieve the optimal therapeutic ratio for patients. Elaborate treatment plans do no good if the implementation is suboptimal, and widespread adoption of quality-assurance/improvement programs integrates radiation therapists, dosimetrists, physicists, and physicians to optimize workflow and ensure patient safety. Ongoing work continues to improve understanding of radiation toxicity in the context of advances in immunotherapy, new surgical techniques, and hypofractionated radiation schedules.[115,174,175] Where possible, we recommend a radiation oncology consultation to assist in the diagnosis and management of RT-associated toxicity; review of RT plans containing organ doses is especially valuable. ■

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