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Chapter

Radiation Injury and Emergency Medicine

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Abstract

The discovery of radiation has led to many advances. Guidelines have been created to minimize radiation exposure and treatment management following both unintentional and intentional exposure. The effects of radiation exposure on specific tissues varies. Tragic consequences can result, ranging from severe, acute injury to long- lasting effects that present years after the initial exposure. In this chapter we provide observations that demonstrate the importance of understanding guidelines to minimize radioactive exposure and the expectations and treatment management following exposure. For the safety and well-being of patients, health care professionals need to remain well-informed to minimize the risks of this tool.

Keywords: radiation injury, emergency care and treatment

1. Introduction

Our understanding of toxicity associated with exposure to radiation has increased since the discovery of X-rays in 1895. X-rays were used to treat a variety of malignant and non-malignant diseases. The effects of radioactive exposure on specific tissues can vary. Radioactive particles destroy or impair tissue by generating free radicals that damage important molecular structures, such as DNA. Radiation exposure can lead to catastrophic consequences, ranging from severe, acute injury to long-lasting effects that manifest years after the initial exposure. This chapter provides observations that demonstrate the importance of understanding guidelines to minimize radioactive exposure, and the expectations and treatment management following exposure [1–3].

Exposure to radioactive particles is divided into intentional or unintentional causes. Notable intentional causes include the atomic weapons activated on Hiroshima and Nagasaki in Japan during World War II. The immediate injuries and fatalities were from the heat and mechanical force generated by the trauma and physical destruction. However, it became apparent that there were longer lasting consequences. Survivors in the surrounding area were exposed to high levels of radiation and suffered from acute toxicity injuries and organ failure. Many of those who did not

succumb to the effects of acute toxicity were known to suffer lifelong chronic conditions, such as developmental problems in newborns and increased cancer risk [4–6].

Unintentional causes are usually the result of radiation exposure without intent to injure. These unintentional causes are typically related to the effects of radioactive materials utilized for energy or medical treatment. The first radiograph was taken in 1895 and early pioneers in the field were unaware of the consequences of exposure. Initial procedures were often associated with unintentional exposure and were fraught with numerous complications such as skin blistering, hair loss and systemic toxicity that we now know were due to radiation toxicity. These signs and symptoms were similar to those present in exposed workers in the first nuclear development programs, many of whom would later develop injuries and cancers as a consequence of their profession [7, 8].

Despite these risks, nuclear power continues to be used for its benefits. Fortunately, we now know much more about how to avoid and minimize radioactive exposure. Rigorous standards enforcing safe practices with radioactive material and the formation of numerous regulatory agencies such as the Nuclear Regulatory Commission are a testament to how far we have come [9]. However, accidents involving radioactive material do occur. In this chapter, we describe a brief history of well-known incidents involving unintended radioactive exposure, as well as the clinical consequences and care of the patient following exposure.

2. Unintended causes: nuclear accidents

One of the most significant nuclear accidents in history was Chernobyl. On that day, a series of missteps during a routine safety check resulted in a massive explosion that sent a plume of radioactive material into the air for an entire week. The range of this explosion extended well beyond the immediate vicinity, exposing other parts of Europe to radioactive gas in the process. In addition to exposing civilians to the radioactive material, first responders also received significant radiation levels and thermal injury, many of which were lethal. More recently, the nuclear reactor in Fukushima, Japan experienced a meltdown following the 2011 tsunami in Japan. While there were no immediate casualties, there was lasting environmental damage and the long-term health consequences are yet to be fully understood [8]. These examples demonstrate the importance of proper safety measures and providing an effective response to nuclear accidents.

3. Acute toxicity

Toxicity from radiation exposure can be divided into three types: acute, subacute and chronic/late. Acute radiation toxicity is defined as signs and symptoms ≤90 days following exposure. In a medical setting, treatment of acute exposure is quite common. During radiation therapy, radiation is targeted and delivered to tumors and management of side effects from the radiation exposure remains a mainstay of modern oncology.

The radioactive dose from these procedures is typically far less than the dose following unintended exposures outside of the clinical setting. The radiation treatment dose is usually fractionated, meaning the dose is given in intervals to reduce the short-term toxicity of the radioactive treatment. The clinical manifestations of acute toxicity following a radioactive accident may be much more severe than those typically encountered by most physicians and may warrant treatment in an emergency setting [4, 5].

Acute radiation toxicity involves many organ systems, including but not limited to the central nervous, gastrointestinal, and cardiovascular systems. Cells with self-renewal potential may be able to recover better from radiation damage compared to those without such protective mechanisms. Self-renewal processes are often accelerated as a response to injury where slowly proliferative tissues cannot. However, if the exposure is given in a single fraction of high enough dose, this ability for self-renewal potential will be overwhelmed. For example, a single total body dose >10 Gy will result in death within days from numerous possible causes. Damage to the central nervous system will result in cerebrovascular syndrome, with uncontrollable swelling in neuromuscular tissue. Despite best supportive care there are no medical interventions to prevent death at this level of exposure. Damage to the gastrointestinal system results in severe diarrhea and associated fluid loss. The mechanism involves depletion of most stem cells within the gastrointestinal crypts. Since these stem cells are required to replace the mucosal surface, these mucosal surfaces will disappear a few days after exposure and there will be no barrier to prevent fluid loss or bacterial entrance into the bloodstream. As a result, patients will typically present with fever, nausea, vomiting, fatigue, anorexia, and severe hypotension. Doses of 4–5 Gy are enough to cause death from depleted stem cells in the hematopoietic system without support. Those that survive the initial depletion typically succumb to infection a month later due to depleted lymphocytes and other immune elements. These manifestations can occur minutes after exposure, with severity being proportional to dose and a sharp decrease in lymphocytes within two days of exposure [1, 4, 5].

Should the patient be exposed to doses below 4 Gy, symptomatic and best supportive treatment is recommended. Nausea and vomiting are the typical initial symptoms and should be treated with hydration. If the exposure dose is unknown, noting the time of onset of vomiting is important as exposure dose is inversely proportional to time to emesis. It is not uncommon for patients at low exposure doses to feel fine for a few weeks before the gastrointestinal and hematopoietic symptoms drive a patient to seek medical care. Upon initiation of care, isolation and contact inhibition is vital since infection is a major contributor towards death in these patients as depletion of the hematopoietic system occurs. Blood transfusion and antibiotics can be delivered to alleviate these issues. A patient will often also present with skin injury burns at the site of radiation exposure as epidermal and dermal injury associated with stem cell depletion can mimic and appear similar to a thermal injury. These injuries should be treated promptly, as they are easy routes for infection to occur, which can be devastating to a patient with a compromised hematopoietic system. In patients with high exposure doses, end of life care is a possible consideration. At an exposure of 5 Gy, only about half of patients will survive after 30 days. An exposure of 10 Gy is considered lethal regardless of medical interventions [1, 5, 6]. Treating patients following radiation exposure is not only challenging in terms of clinical aspects, but emotionally as well.

Compounds that have been developed to reduce and even prevent the clinical manifestations following radiation exposure are called mitigators. These compounds work by altering the molecular response following radiation exposure. As such, a mitigator could inhibit lymphocyte recruitment at sites of radiation damage, increase proliferation of stem cells that would normally be inhibited by radiation exposure, or inhibit fibrosis. An example of a mitigator is Palifermin, a growth factor that stimulates cell growth in response to radiation exposure to reduce recovery time. Radioprotectors, on the other hand, are given before or immediately after radiation exposure to protect against the effects of radiation toxicity [10, 11]. Amifostone is one such radioprotector that has been approved by the FDA for reducing side effects from radiation therapy [12]. More mitigators and

radioprotectors are expected to be approved as the need to protect against radiation toxicity increases. Although many compounds have been and are in development, no others to date are actively used in clinical practice and the role of both hematopoietic and mesenchymal transplant remains under investigation.

4. Subacute and late toxicity

The subacute and/or late effects of radiation toxicity, by nature, are less visible and harder to identify for most emergency and primary care physicians. Often, these effects take many years to develop and are often mistaken as sequelae from another disease. However, they are nevertheless important to identify and address. A common misconception is that the degree to which a patient suffers from acute symptoms is proportional to severity of the long-term response. Unfortunately, patients who experience little to no acute sequela can experience serious long-term sequela, and vice versa. While both children and adults can experience the effects of late radiation toxicity, children are susceptible as they have a much longer period for these clinical manifestations to develop [13]. Unlike acute toxicity effects, anticipating long term effects is much more difficult. This technique relies heavily not only on a physician's knowledge of potential long-term effects, but also their willingness to investigate a potential long-term effect.

5. Organ specific injury

A common theme in radiation injury is the ability of the tissue or organ to respond to cell death and self-regenerate. These aspects vary among organs and thus the clinical presentation and treatment is different depending on the organ involved. Injuries and treatment protocols for specific organs are as follows:

5.1. Hematopoietic system

As previously discussed, damage to the hematopoietic system typically results from injury to progenitor cells, which can lead to hematopoietic crisis and infection. Fortunately, with the exception of whole-body exposure, the hematopoietic system is generally able to recover from radiation damage due to migration of stem cells from outside the site of exposure. Patients who are also receiving chemotherapy or taking medications that may result in immunosuppressed states should be carefully assessed. In the case of total body irradiation, an immediate decrease in circulating lymphocytes can be expected with subsequent defects in immune response. Symptomatic treatment, including blood infusions and antibiotics as needed, with isolation are crucial in these situations [13, 14]. Use of bone marrow transplants to replenish depleted progenitor cells has a theoretical survival benefit opportunity in total body irradiation patients, but to date has not been embraced as standard practice and often only applied to those most severely affected. The risk of graft-vs-host disease makes this approach controversial, especially in the setting of an emergency unrelated allogeneic transplant [6].

5.2. Skin

The skin is often the most direct site of radiation injury, as the epidermis covers all other organs and is susceptible to radiation damage. The dermal stem cells are the most susceptible component of the skin, as these are the actively dividing cells

that replace other cells in the rest of the organ. Early symptoms of exposure typically involve erythema and swelling as vasodilation and the recruitment of inflammatory components localize to the area. These symptoms typically resolve within a month. Late term effects include decreased wound healing capacity with increased fibrosis and ulceration. Interestingly, the skin will appear to be more vascularized with more prominent vasculature. However, this is due to thinning of the epidermis, which causes veins to appear more prominent. Proper wound care is the standard treatment for these manifestations, with surgical debridement as needed. Particular concern must be paid for patients with medical conditions that are prone to fibrosis, such as those with dermatitis, lupus, and scleroderma. Skin infections, such as cellulitis, are particularly dangerous given the immunosuppressive effects of radiation therapy. Lastly, an interesting phenomenon occurs in some patients where previously irradiated skin can become erythemic and fibrotic several years later in response to certain medications like antibiotics and chemotherapy. The mechanism behind this phenomenon is unknown [15].

In the past, skin involvement from radiation therapy that could not be treated with topical ointments was relatively rare. However, with the increasing use of hypofractionation (radiation therapy with greater amounts of dose per treatment), these findings are becoming more common [16]. Thus, radiation damage to the skin is likely to become more prominent in the future as therapy becomes more compressed with higher doses delivered in a shorter period of time. Patients with a history of radiation therapy and significant skin sequalae should be carefully observed for more serious developments as injuries in treated tissues heal less well and contain less local immunity.

5.3. Gastrointestinal system

Like the skin, the gastrointestinal system is composed of mucosal cells with multiple layers underneath that are constantly replaced over time. Unfortunately, the rate at which some of these cells are replaced is higher than that of the skin, leading to more immediate and sometimes more severe clinical manifestations. Cells of the gastric and small bowel tend to have the highest rate of replacement, leading to very early nausea if these regions were exposed. Exposure to mucosal cells in the upper gastrointestinal system (mouth, esophagus, salivary glands) tend to present with clinical symptoms around two weeks after exposure due to a longer replacement rate. Damage to these cells tends to present with more localized pain and swelling. Exposure to the salivary glands can result not only with localized pain, but also xerostomia (dryness of mouth) and ageusia (loss of taste). Saliva can become more acidic which can further injure normal tissue and alter the environment of the oral cavity. Regardless of these manifestations, patients should be advised to maintain adequate nutrition and dental hygiene, as this practice helps mitigate the complications of an immunocompromised state. Symptomatic treatment of localized pain is also advised and considered standard of care as bone exposure can be a serious consequence of mucosal denudation [14]. **Figure 1** represents modern head/neck radiation therapy treatment plan through the oral cavity demonstrating sparing of the parotid tissue with intensity modulation.

Farther along the digestive tract, the expected symptoms can be predicted based on the location of the tumor. Radiation exposure to the gastric mucosa during treatment of gastric tumors can result in near immediate nausea given the daily replacement the gastric mucosa. Treatment of esophageal tumors, which are now more commonly in the lower third of the esophagus, present with a timeline of symptoms similar to head and neck tumors (approximately two weeks after exposure). Tumors in this region typically cause dysphagia and anorexia. Treatment initially tends to relieve patient symptoms, but later patients may return thinking the tumor

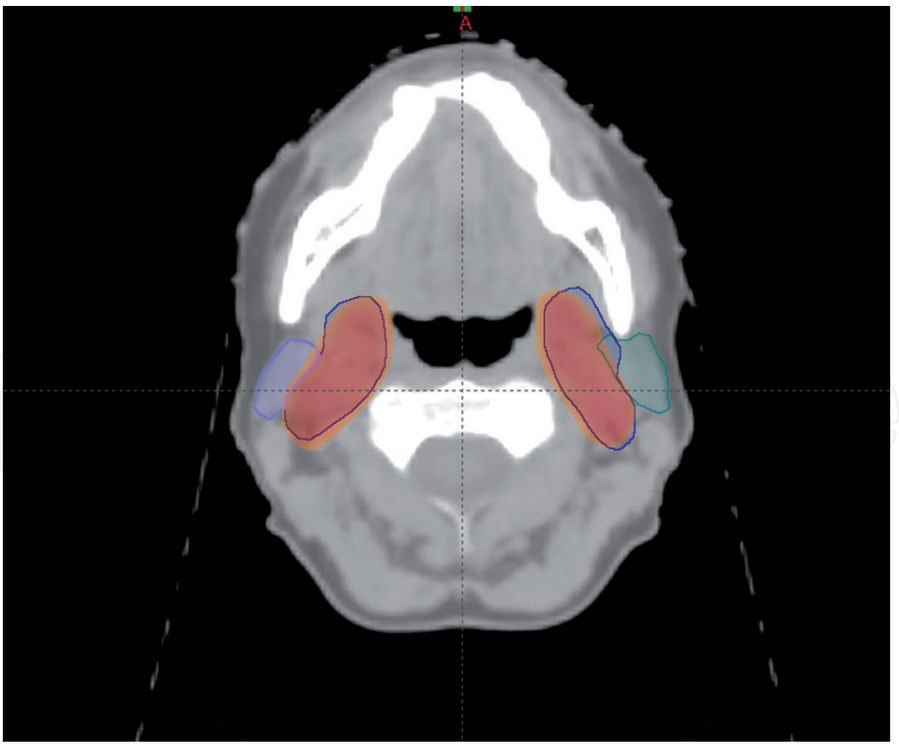

Figure 1.
Parotid sparing. Image courtesy of the Department of Radiation Oncology, University of Massachusetts Medical School.

has returned when in reality these symptoms are due to swelling from the therapy. Like head and neck tumors, patients should be advised to continue maintaining adequate hydration and nutrition [13, 14].

Symptoms from radiation exposure in the small and large bowel are more complex and require more in-depth patient history and laboratory tests. The small bowel absorbs much of the nutrients from food. Damaging the microvilli of the mucosal surface, which are vital for nutrient absorption, can result in severe malabsorption regardless of a patient's appetite. These findings can be confirmed by stool tests. Patients will often present to the emergency room with diarrhea, steatorrhea, bloating and general abdominal pain a few days after radiation exposure. The large bowel plays an important role in absorption of water, and exposure of large portions of this organ may compromise this function. Patients may complain of increased defecation frequency, which can lead to dehydration and electrolyte abnormalities that can be confirmed through electrolyte panels. To make matters more difficult, abdominal organs are prone to forming adhesions after surgical interventions, which disrupts blood flow to portions of the bowel that are exacerbated after concurrent radiation therapy. Anticipation of these issues through a careful patient history are vital to preventing severe complications from occurring [13, 14, 17].

Late effects of radiation also depend on location of the exposure. The mucosal cells of the oral cavity should theoretically recover like that of typical skin cells, but the combination of a tight space and harsh oral environment prone to infection and necrosis makes healing difficult. Thus, fibrosis and ulceration over a long period of time are possible. Acute effects of radiation typically damage mucosa of the gums and affect the pH of the saliva, facilitating microbial growth. These changes can lead to long-term problems with dental hygiene and patients should modify their dental habits accordingly through increased tooth brushing and fluoride mouthwash [13, 14]. Motility issues are also becoming more common, especially since patients who receive radiation therapy are now living longer. Dysphagia appears to be due to edema surrounding constrictor muscles, and physical therapy

to encourage lymph drainage offers symptomatic treatment [18]. Gastric emptying issues due fibrosis at the gastric antrum and regions in the bowel where surgery was performed are also possible years after treatment. Atrophy of the pancreas many years after radiation exposure is also known to happen, although the clinical relevance of this is unknown [13, 14]. Symptoms can mimic malabsorption syndrome.

5.4. Lung

The main mechanism of radiation injury in the lungs is the generation of free oxygen and nitrogen radicals which damage the lung parenchyma with irregular repair of type I and II pneumocytes along the delicate reticulin network of pulmonary parenchyma. This oxidative damage causes disorganized repair and replacement of these cells associated with late fibrosis, impairs the ability for the lungs to oxygenate the blood. Pneumocyte damage also leads to recruitment of pro-inflammatory modulators that recruit immune cells to the region, leading to fibrosis and further depleting oxygenation capacity [19]. Furthermore, the radiation-driven production of nitric oxide has been suggested as a possible cause of damage to lung parenchyma outside of the field of radiation [20].

Complicating this situation is that many chemotherapeutic agents given with radiation therapy, such as bleomycin, also causes pulmonary fibrosis. The results of these sequelae are the development of pneumonitis up to two to six months after exposure. If asymptomatic, careful observation is standard of care. If symptomatic, the patient usually presents with occasional bouts of cough and dyspnea. Treatment with corticosteroids, supplementary oxygen, and prophylactic antibiotics are recommended in this situation. Once the pneumonitis resolves, fibrosis typically marks the site of radiation injury and can result in limited ventilation requiring long term use of supplemental oxygen. Given these findings, it is important to note that these patients tend to be at higher risk of developing chronic pulmonary disease compared to those who were unexposed [13, 21–24]. Pulmonary rehabilitation is an important aspect to survivorship care and optimizing respiratory health is important to each patient as the rehabilitate from therapy. **Figure 2** represents changes in lung parenchyma associated with immunotherapy and low dose radiation therapy with improvement seen after withdrawal of the immunotherapy.

5.5. Liver

Radiation injury to the liver, also known as radiation-induced liver disease (RILD), is unique in that it is often during the healing process that tissue function undergoes disorganized repair, including injury to the reticulum network, and limits the vascular relationship to the hepatocyte. While acute damage to hepatocytes affects liver function, as the cells divide during repair they tend to become disorganized, particularly if the structural reticulum of the liver is damaged. Increased distance between the hepatocytes and the blood supply leads to decreased liver function. This phenomenon explains why the state of the liver before exposure to radiation also plays an important role in this process. For example, a cirrhotic liver due to heavy alcoholic use or hepatitis will likely have pre-existing disorganized architecture, making this liver more susceptible to radiation damage. This includes veno-occlusive disease which also separates vascular anatomy from the hepatocyte. For these reasons, imaging studies such as magnetic resonance imaging before the delivery of radiation are obtained for evaluation of anatomy and function [25]. Disorganized repair can lead to migration of infusional therapies including radiolabeled therapy as the vascular anatomy can be disrupted and limit efficacy in spite of placement of therapy in close approximation to disease.

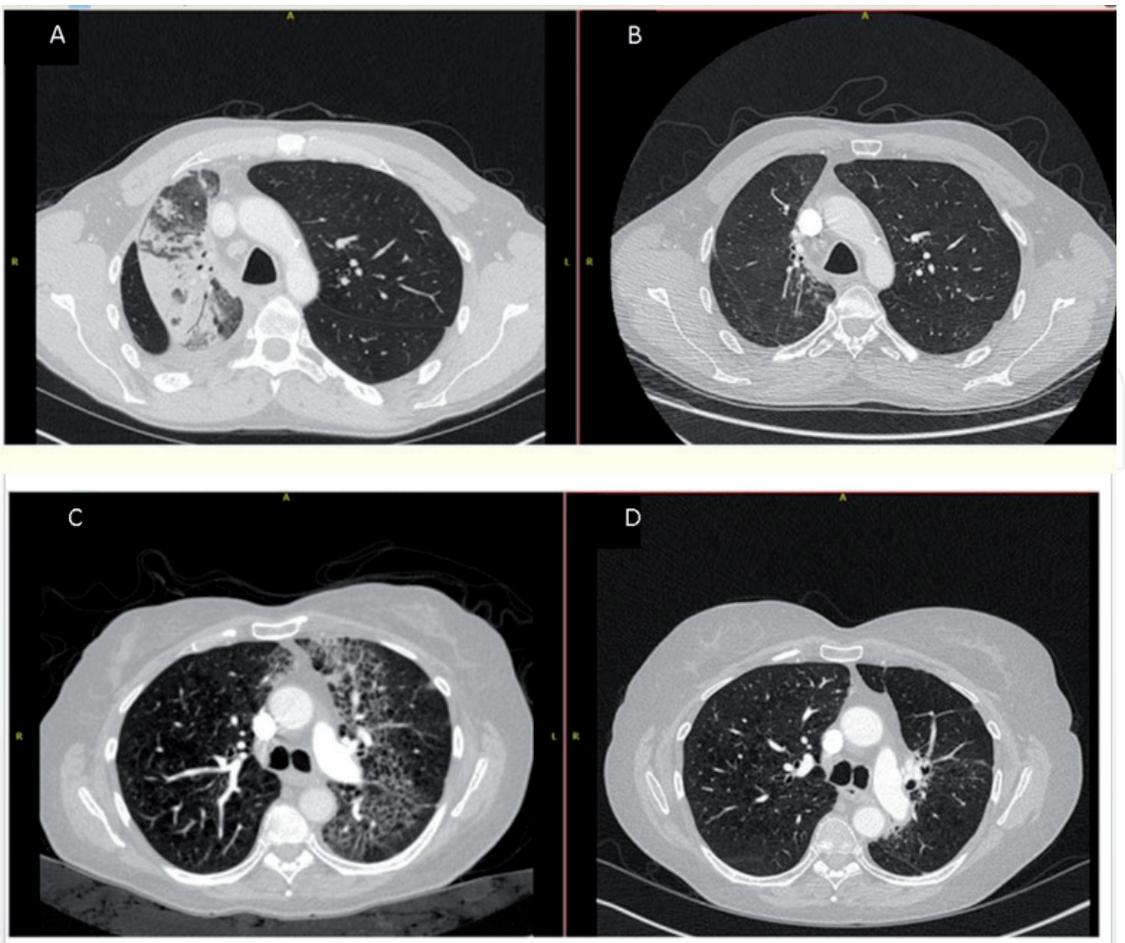

Figure 2.
(A) and (C) Therapy driven pneumonitis outlining the radiation therapy field while on immune check point inhibition. (B) and (D) Improvement after immunotherapy withdrawal. Courtesy of the Department of Radiation Oncology, University of Massachusetts Medical School.

Patients with RILD typically experience symptoms that mimic cirrhosis, which include abdominal pain, elevated liver enzymes, jaundice, and ascites within four months of radiation exposure. Livers with pre-existing damage typically have earlier onset, with more severe symptoms. Treatment is symptomatic with keen observation of potential veno-occlusive and metabolic disease secondary to a congested liver with decreased function. Careful consideration must be given for medications that are metabolized in the liver, especially chemotherapeutic agents that are also hepatotoxic [25, 26].

5.6. Renal

All components of the kidney, including structures crucial for filtration, such as cells of the glomerulus, are susceptible to radiation damage. The signs of acute radiation damage are usually seen within 3–18 months, typically mimicking signs of renal failure. These signs include decreased glomerular filtration rate (GFR), increased serum β2-microglobulin, albuminuria, and other markers of poor renal function. Later signs of kidney radiation damage, which include hypertension and eventual renal failure, are often hard to distinguish from other pathological causes. For treatment of these sequelae, the use of hypertension medications such as angiotensin-converting-enzyme inhibitors (ACE) inhibitors are theoretically beneficial. Monitoring of renal function, both short and long term, also remains crucial in the standard of care for these patients [27–29]. In aging patients who are

not candidates for surgery, radiation therapy with stereotactic techniques is being used more frequently to treat sub-total renal volumes for renal malignancies in an effort to spare as much renal function as possible.

5.7. Cardiovascular system

The mechanism of radiation damage to the heart and blood vessels involves immediate cellular damage followed by fibrotic and disorganized repair, leading to reduced function in all cardiac segments including electrical conduction, myocardium, valves, and vascular anatomy. The time period is variable due to differences in size and functional architecture. However, what is clear is that unintended radiation exposure to the heart and blood vessels has a strong association with cardiovascular disease and complications [30–33]. The lack of mitigation and therapeutic strategies in response to radiation of cardiovascular tissues explains why radiation oncologists spend such a large amount of effort to minimize cardiovascular exposure [34].

Generous radiation exposure to the heart can result in acute pericarditis. This diagnosis should always be in the differential in a patient with history of radiation exposure who presents with sharp, radiating chest pain that is relieved when sitting up. Anti-inflammatory medications like aspirin, colchicine and prednisone can offer symptomatic relief, with pericardiocentesis being an option in severe cases. Long term, patients who receive radiation exposure to the heart have a higher risk of heart disease and use of echocardiograms and nuclear stress tests in these patients is recommended if symptoms warrant use. Large blood vessels like the aortic, carotid, and femoral arteries can experience hyperplasia and atherosclerotic change from radiation doses. These changes can result in rupture and fistula formation, necessitating immediate treatment. This usually requires very high doses and prolonged exposure usually not seen in modern radiation therapy [30–33]. With improvements in survival, patients can receive therapy with intentional overlap to previously treated volumes for second malignancies. These patients are vulnerable to vascular injury, including larger arteries and survivorship plans need to include periodic surveillance of vessels to optimize follow up care. **Figure 3** demonstrates cardiac sparing for left-sided breast cancer treatment with breath-hold treatment techniques and optical tracking.

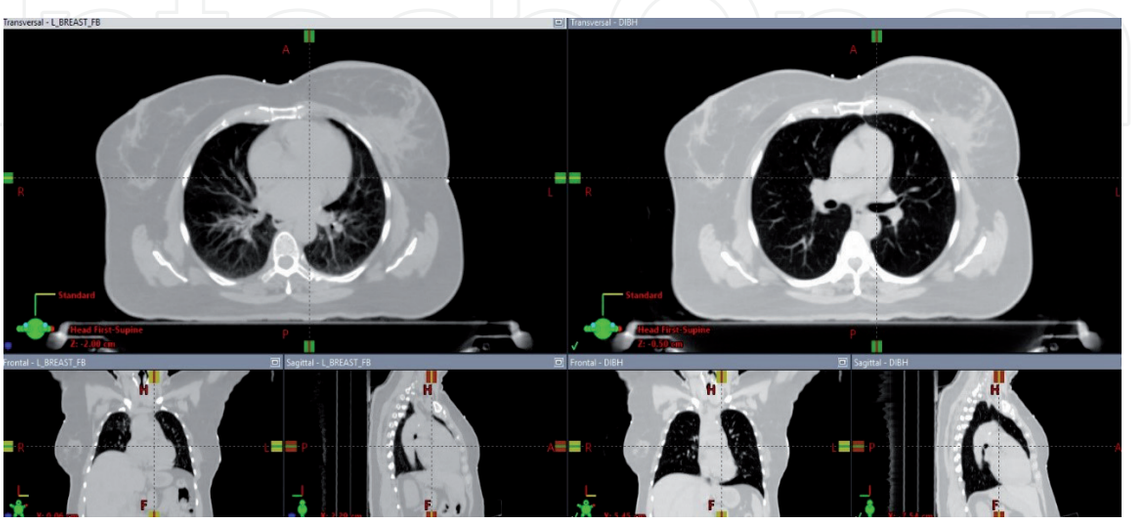

Figure 3.
Cardiac sparing with deep inspiration breath-hold (DIBH), (left-free-breathing (FB); right-DIBH). Image courtesy of the Department of Radiation Oncology, University of Massachusetts Medical School.

5.8. Nervous system

Since most cells of the nervous system do not typically have a high turnover rate, it would seem reasonable to assume that the nervous system is more resistant to radiation damage than other organs. However, this assumption does not account for the immediate molecular effects of radiation. Regardless of the rate of cell division, all cells will receive damage to membranes, organelles, and other structures within the cell. Cells that do not divide very frequently will have to endure these injuries for long periods of time, leading to eventual clinical manifestations. Damage to nearby vasculature also limits growth and healing of these structures, leading to pronounced long term effects. There are clear reports of radiation damage to the central nervous system sometimes long after the initial radiation exposure [35–38].

Patients who received radiosurgery or hypofractionation techniques are at risk of developing necrosis within six months of receiving therapy. Clinically, these developments can result in focal changes and change in behavior depending on the site of necrosis. Demyelinating syndromes, although rare, are also possible in the peripheral nerves and spinal cord. Often, neurotoxic symptoms are enhanced by chemotherapeutic agents, such as vinblastine, vincristine and cisplatin. Gathering a detailed physical exam, medical history and possible neurological referral may be required for definitive identification of these outcomes. Patients who received radiation therapy for pituitary adenomas or at sites near the optic structures are at risk for visual changes [36, 37]. This is because some structures, such as the lens and optic chasm, are sensitive to radiation exposure due to limited blood supply [15, 39, 40]. Patients treated for breast and head and neck cancers may rarely present with brachial plexopathy. Peripheral lymph nodes for these regions are often within the same field of treatment as the brachial plexus, resulting in unintended exposure to this region [41].

5.9. Endocrine

The effect of radiation therapy on the endocrine glands varies depending on the gland affected. The timeline for the development of clinical sequelae varies, with some cases even being reported many years after the radiation exposure. The pituitary gland is relatively radiation sensitive and results in panhypopituitary syndrome, requiring supplementation of depleted hormones. Secondary malignancies from un-intentional radiation exposure, while rare, have been reported [42]. Patients who received previous head and neck radiation therapy who now present with headache, vision loss and/or hormonal abnormalities should be carefully examined for the development of pituitary adenomas. The thyroid gland is also sensitive to radiation therapy, resulting in hypothyroid syndromes. Patients who receive radiation therapy to the head and neck often receive surgery that involves dissection of the thyroid gland, exasperating thyroid function loss. The thyroid also has a relatively higher incidence of developing secondary malignancies. This finding has been identified not only in patients receiving radiation therapy, but also victims of the Chernobyl incident [5]. The same care must be given to the parathyroid glands, given the proximity to the thyroid gland, which can present with signs and symptoms of hypoparathyroidism. Radiation exposure to the endocrine pancreas and adrenal glands are less characterized and are thought to be more radiation resistant. However, there are a few cases of injury to these organs associated with radiation exposure [42].

5.10. Reproductive

The reproductive organs are highly sensitive to radiation damage, with early exposure in pediatric patients leading to severe detriments like sterility and

secondary malignancies (see Pediatrics). Since much of the reproductive system depends on hormonal homeostasis, radioactive effects on the endocrine system (see Endocrine) and the subsequent effect on hormone production, such as that on testosterone and estrogen, can drastically affect reproductive function and development depending on the effected hormone and gland. When investigating radiation injury to the reproductive system, it is always important to consider the location of exposure and any endocrine glands involved. Germ cells, such as spermatogonia, are particularly sensitive to radiation damage as they can experience inter-mitotic death. Even mild radiation exposure can lead to a heavy drop in sperm numbers. Mature sperm that receive radiation damage can harbor serious mutations or chromosomal abnormalities, leading to severe birth defects in progeny. Exposure to female reproductive organs can even lead to miscarriage and early menopause. As a result, it usually recommended for patients who receive gonadal exposure practice birth control methods for up to six months after the exposure. Because the ovaries rely on a regular, cyclical production of hormones from the follicles, radiation injury can lead to more pronounced effects on fertility. Mucosal atrophy and drying of female genitalia can cause great discomfort for the patient as well. Thus, fertility treatment and consultation should be considered for patients who received heavy or repeated radiation exposure to the gonads [13, 14, 42].

6. Pediatrics

Pediatric patients are unique in that many organs and tissues are still developing. As a result, the cells involved are particularly sensitive to radiation damage as the fully developed adult organ can become abnormal or dysfunctional. Pediatric patients who receive radiation therapy are known to have a higher risk of developing growth abnormalities, chronic diseases, secondary malignancies and premature death compared to sibling controls [43]. Children who were treated with radiotherapy in the pelvis for tumors such as rhabdomyosarcoma or germ cell tumors are at high risk for gonadal abnormalities. Given the rapid growth in the musculoskeletal system during puberty, exposure to the spine at an early age can cause drastic changes to the respiratory and cardiovascular system. Radiation exposure to any cartilage or bone not only presents the risk of bone necrosis, but also may affect the fully developed form of such tissue, sometimes resulting in stunted extremity length and increased frequency of fractures. Children treated for Wilms tumors are at high risk of renal abnormalities later in their lifetime to the remaining kidney, therefore attention to detail for renal health as these patients become adults is an important aspect of a survivorship plan. Exposure to the bowel and hepatic structures are known to adversely affect the growth and development of intraabdominal organs. These effects can affect nutritional intake, indirectly causing developmental issues as the child matures [14, 43, 44]. As these patients mature into adulthood, detailed review of a patient's radiation exposure history will play a pivotal role in survivorship plans.

7. Mitigation strategies in planning

As many of the side effects of radiation therapy are difficult to anticipate and manage, a great deal of effort has been put into reducing the amount of non-tumor tissue exposed to radiation. In the early days of radiation, this was difficult simply due to the lack of technology. Now, most radiation oncologists have access to various new tools, such as 4-dimensional conformal avoidance techniques to minimize

off-target exposure [34]. Compact structures that were traditionally difficult to irradiate without significant off-target, such as the axilla and chest, can now be treated much more accurately with minimal exposure to non-tumor tissue [41]. Modern imaging techniques can be utilized to assess organ performance even before the administration of radiation to determine the risk of post-radiation symptoms. Indocyanine retention assays used in conjunction with MRI have determined the pre-exposure function of liver to assess if the patient is a good candidate for radiation therapy [25]. New guidelines are constantly being updated to ensure that the risks of radiation therapy are minimized. Novel pharmacological agents, such as the development of immunotherapy, are being implemented to supplement the efficiency of radiation therapy. As medicine becomes more collaborative and data is more available, physicians outside of radiation oncology will be able to better understand the radiation therapy treatment plans and define survivorship care plans accordingly.

8. Conclusions

The discovery of nuclear power and the utilization to benefit humanity has been one of the defining moments of the modern era. While this discovery certainly has benefits, there are also unintended and intended consequences which we must continue to mitigate. In the field of medicine, what is clear is that radiation remains a crucial tool to diagnose and treat diseases. Understanding and minimizing the risks of using this tool remains a priority for the safety and well-being of patients, especially given the broad impact it has on organs throughout the body and the long-term effects. It falls upon health care professionals to remain vigilant and well-informed to ensure that nuclear energy and radiation therapy remains a blessing and not a curse.

Conflict of interest

The authors declare no conflict of interest.

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