Review Article Outline: Secondary Malignancies Following Radiation Therapy

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Abstract

Around 40% of the population will receive a cancer diagnosis at some point in their lifetime, and of those patients, 50% will receive radiation therapy as part of their care. Radiation therapy can be implemented in the definitive setting with curative intent or in the palliative setting to alleviate symptoms. Although integral in care, there are long-term risks after radiation therapy, namely the low likelihood of developing a secondary malignancy. This risk is small, much less than 1%; however, can be consequential. Established risk factors such as age at the time of treatment, gender, and radiation technique are important factors when calculating an individual's risk. To mitigate the likelihood of secondary malignancy, several strategies such as choice of radiation technique (i.e., protons, MRI-guided radiation therapy) and decreased frequency of on-board imaging can be considered. Importantly, patient and provider education regarding changes in cancer screening to detect secondary malignancies at an early stage are critical. Secondary malignancies following radiation therapy are rare; but recognizing the risk factors and strategies to mitigate these risks can prevent patients from experiencing this serious iatrogenic complication.

Introduction

Cancer Incidence

Cancer remains a significant public health challenge, affecting millions of individuals worldwide. The estimated new cases and deaths from various types of cancer provide a sobering snapshot of the current burden of this disease. In the United States, prostate cancer is the most frequently diagnosed cancer among males, accounting for 21% of new cases, while breast cancer leads in females with 29% of new cases. Lung and bronchus cancers follow closely, representing 14% and 13% of new cases in males and females, respectively, but are the leading cause of cancer-related death in both genders.[1] These statistics underscore the critical need for effective treatment strategies and ongoing research to improve patient outcomes.

Treatment Modalities

Treatment modalities for cancer have evolved significantly over the years, incorporating a range of approaches including surgery, chemotherapy, and radiation therapy. Multimodal treatment, which combines these methods, is often employed to enhance therapeutic efficacy and improve survival rates. Radiation therapy, a cornerstone of cancer treatment, can be delivered through internal (brachytherapy) or external beam radiation. Brachytherapy involves placing radioactive

sources directly within or near the tumor, while external beam radiation (EBRT) uses high-energy waves to target the cancer from outside the body.

The underlying mechanism of radiation therapy involves the use of the electromagnetic spectrum to induce DNA double-stranded breaks in cancer cells, leading to cell death or impaired replication. Despite its effectiveness, radiation therapy carries a risk of secondary cancers due to DNA damage of nearby healthy tissues.[2] Chemotherapy also portends a secondary cancer risk, most frequently in the form of hematologic malignancies. Understanding these risks and refining treatment protocols to minimize adverse effects are critical areas of ongoing research in oncology. As scientific and clinical efforts continue to treat and prevent cancer, integrating advanced technologies and personalized treatment plans holds promise for more effective and safer cancer care.

Radiobiology

Understanding the radiobiology of ionizing radiation is important as it plays a role in the development of secondary malignancies. There are two types of ionizing radiation: excitation in which the electron is raised to a higher energy level without ejection of the electron or ionization, in which an electron is ejected and energy is dissipated. Absorption of this energy can be directly ionizing or indirectly ionizing. Direct ionizing radiation “directly” causes damage to the atomic structure of the molecule whereas indirectly ionizing x-rays give their energy off to a fast-moving uncharged particle such as a neutron which then produces damage.

When ionizing radiation hits double-stranded DNA during treatment delivery, the majority of damage is through indirect action. This occurs when the radiation hits a nearby particle (close to the DNA), typically water, and then creates a free radical which then goes on to damage DNA. The most commonly produced free radical is a hydroxyl ion (OH).

When DNA is damaged, there are different natural repair pathways put forth such as base excision repair, single-strand break repair, double-strand break repair and mismatch repair. If the DNA is not properly repaired, this can result in abnormalities within the chromosome, which can eventually result in death (i.e. apoptosis) of the cell.

The risk of developing a secondary cancer is dependent on the dose rate (i.e. how much radiation is received in what amount of time). It also varies by organ, in which the bladder, breast, lung, and thyroid are at the greatest risk of secondary cancer development given the biology of these tissues. Carcinoma and leukemia are more likely to develop in the tissues of individuals exposed to low doses of radiation therapy. This is in contrast to sarcoma, which is more likely to develop in the high-dose regions of the prior radiation plan.

Secondary Malignancy

Secondary malignancies are a rare complication of radiation therapy; however, there are specific and known risk factors that may amplify an individual's risk. For a cancer to be deemed

a secondary malignancy as a result of prior radiation therapy, specific criteria must be met to make the diagnosis. These criteria are often referred to as the Cahan criteria. Tumors must arise in the prior irradiated field with an appropriate latency period (preferably greater than four years) and be biopsy-proven in tissue that was previously normal before receiving radiation therapy.[3]

Of all these risk factors, the age of the patient at which they undergo radiation therapy is the most influential factor, with children being 10 times more sensitive to secondary malignancies compared to adults due to their longer latency periods.[4] For example, patients treated in their teens would theoretically have more years to live and subsequently, more time to develop a secondary malignancy. Gender is another important factor, as women face a higher risk than men, partly due to a higher incidence of breast cancer which is often diagnosed in younger patients. Data from the atomic bombings further supports this gender disparity, demonstrating a 35% increase in risk for men and a 58% increase for women per Gy of radiation exposure.[5] Additionally, there is a temporal association in the development of secondary malignancies, with radiation exposure initially causing leukemia in atomic bomb survivors, followed by the emergence of solid tumors years later.[6]

Specific radiation techniques such as intensity-modulated radiation therapy (IMRT), have been associated with an increased risk of secondary malignancies as there is a higher volume of low-dose bath to more normal tissue compared to 3D conformal radiation therapy (3D-CRT). Another theory in which radiation therapy may result in an increased secondary malignancy risk is not through the treatment itself, but via image-guided radiation therapy (IGRT) which further introduces radiation exposure to normal tissues during setup verification. Techniques like daily portal imaging or megavoltage (MV) cone beam computed tomography (CBCT) can result in exposures of up to 100 mGy per day, heightening the long-term risk of secondary malignancies.[7] In contrast, proton beam therapy (PBT) has shown a reduced risk compared to photon therapy, with a lower crude rate of secondary malignancies—5.2% versus 7.5%—due to the Bragg peak effect, which limits radiation dose deposition beyond the target area.[8]

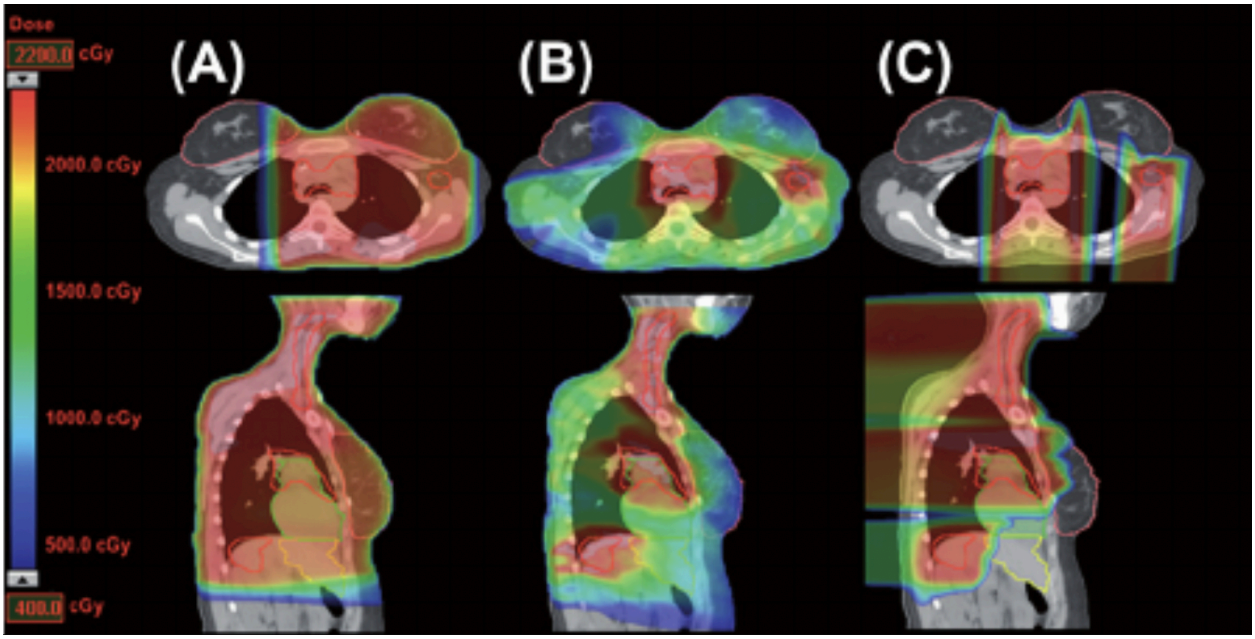
There are additional patient factors that may compound an individual's risk such as prior or current smoking history, hormonal states such as early menopause, and potential hereditary and germline predispositions.

Case Report

Hodgkin lymphoma (HL), frequently diagnosed in adolescence, is often treated with a combination of chemotherapy and radiation therapy. However, radiation therapy and chemotherapy, while effective in controlling the primary disease, can be associated with significant long-term risks. Breast cancer is well-established as the most common secondary

malignancy among female survivors, likely due to the radiation fields used to treat the thoracic area, exposing radiation to nearby healthy breast tissue (Figure 1). Additionally, other secondary malignancies such as thyroid cancer, lung cancer, and gastrointestinal cancers are prevalent. Each anatomical disease side is associated with specific radiation fields and techniques that are employed during treatment. In a long-term comparative study, over 1,000 pediatric HL survivors were followed for nearly three decades and it was demonstrated that survivors were over ten times more likely to develop secondary malignancies compared to the general population.[9]

Figure 1. The Radiation Plan in a Pediatric Patient with Advanced Stage Hodgkin's Lymphoma using 3D-CRT techniques (A), Intensity Modulated Radiation Therapy (B), and Proton Therapy (C)[10]



In this case report, we present a 44-year-old premenopausal patient. She was diagnosed with the classical nodular sclerosis subtype of HL at the age of 24 and treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy and radiation therapy. She was treated with extended radiation therapy fields to both the supra- and infra-diaphragmatic regions with a localized boost to 50 Gy to the left neck nodal regions.

Around 20 years later, the patient was noted to have an ulcerated and fungating right breast tumor. This was biopsied and confirmed as a grade 2 infiltrating ductal carcinoma (IDC) with positive estrogen and progesterone receptor expression. After a multidisciplinary review, this new breast cancer most likely represented a secondary malignancy following her prior radiation

therapy and chemotherapy treatments for HL. After neoadjuvant chemotherapy, she underwent a mastectomy, followed by chest wall radiation therapy and hormone therapy with Tamoxifen.[11]

This case report highlights the vulnerability of pediatric and young adult cancer patients in developing secondary malignancies due to their extended lifespan and the prolonged latency period allowing these cancers to develop. In our patient, her secondary breast cancer developed two decades after her first extended field course. The median time to the onset of a secondary malignancy was approximately 19 years, underscoring the long-term nature of the risk. This prolonged latency period emphasizes the critical importance of lifelong surveillance and follow-up care for survivors of childhood cancers. For this patient in particular, it is known that her risk of breast cancer is heightened. The North American Children's Oncology Group, Dutch Childhood Oncology Group, and the UK Children's Cancer and Leukemia Group have put forward a set of screening guidelines suggesting female survivors of childhood and young adults treated with chest radiation undergo clinical breast exam (CBW), mammography, and breast magnetic resonance imaging (MRI) at the age of 25 years old or eight years after completion of radiation therapy (whichever is soonest).

In summary, this case study underscores the significant long-term risks of secondary malignancies in pediatric Hodgkin lymphoma survivors who have undergone radiation therapy. It highlights the need for ongoing research in safer treatment modalities and the importance of integrating survivorship care into the treatment planning process at consultation. Strategies for early detection and prevention of secondary malignancy are essential for healthcare providers working with this vulnerable population.[9]

Mitigation of Secondary Malignancy Risk

Recent advances in radiation techniques have created more conformal and targeted radiation plans with steep dose drop-off, delivering the prescribed high therapeutic doses to specifically the target. However, this comes at the cost of delivering lower doses of radiation to a higher volume of normal, healthy tissue. One way to mitigate secondary malignancy risk is through the choice of radiation technique and use of 3D-CRT instead of IMRT which results in a lower normal tissue volume of low dose bath. A second way to mitigate risk is through the use of proton therapy. By reducing out-of-field dose via the Bragg peak, the amount of radiation traveling through normal tissues is lower, which is particularly important in pediatric patients who are already at higher risk due to their growing tissues and longer latency period.[12] Proton therapy is most beneficial in treating patients with central nervous system (CNS) tumors in which protecting the brainstem is critical.

On-board imaging with the use of IGRT typically takes in the form of cone-beam CT (CBCT) scans prior to each fraction, increasing a patient's radiation exposure by about 100 mGy per day. One way to reduce this marginally small risk is by imaging less frequently with CBCTs; for example, obtaining a CBCT prior to every two to three fractions instead of each fraction. CBCT

can be replaced with alternative imaging techniques such as KV imaging which exposes the patient to a significantly less amount of radiation dose and can be equally as effective as CBCT in select scenarios. A recent advancement in radiation is the use of MR-guided radiation therapy (MRgRT). Instead of using conventional CT scans as a form of IGRT, patients are treated and imaged with MRI prior to each fraction and oftentimes during the fraction. This is a huge advantage as there is no additional radiation dose from using MRgRT and imaging can be kept on during the entirety of treatment, detecting and allowing for correction of intrafractional variation.

Another way to mitigate risk is by simply being vigilant regarding the importance of surveillance. By being consistent with imaging scans after radiation has been administered, a secondary malignancy has a high chance of being detected in the earlier stages and, therefore, easier to treat. For those treated with radiation therapy, screenings should be tailored to the specific areas that received radiation, ensuring that any secondary malignancy is caught as quickly as possible. Examples of screening modalities include blood tests to check for tumor markers, or obtaining screening scans at an earlier age in shorter intervals.[13] Early detection is key to improving outcomes in patients who may be at risk of developing secondary cancer. Some examples of earlier detection include earlier mammograms in patients who have received radiation therapy to the chest, or earlier screening colonoscopies in patients who have received radiation therapy to the pelvis.

Patient Advocacy

Many cancer survivors worry about developing secondary cancer, which affects 1-3% of survivors. To minimize this risk, follow-up care and healthy living are crucial. Survivors should work with healthcare providers to create a survivorship care plan that includes regular screenings, health check-ups, and personalized care. Understanding individual risk factors, such as age, treatment type, family history, and lifestyle choices, is key, as well as maintaining a healthy lifestyle by avoiding tobacco, eating well, and exercising. Knowing family history can also guide prevention strategies. Recognizing symptoms like lumps or unexplained weight loss is important for early detection. Managing fear of recurrence requires emotional support through cancer support groups, which provide a safe space to share experiences and coping strategies. Open conversations with loved ones and professional counseling can also help. A proactive approach with regular monitoring, health-conscious living, and involvement in support groups improves quality of life and may reduce the likelihood of developing secondary cancer.[14]

Conclusion

While radiation therapy remains a critical tool in cancer treatment, (with approximately 50% of cancer patients receiving radiation treatment) its long-term risks, particularly the development of

secondary malignancies cannot be overlooked.[15] As a result of improved modern therapies, there is an increasing cancer survivor population, many of whom have received radiation therapy as part of their care. Factors such as patient age, gender, radiation dose, and the type of radiation therapy used all contribute to the likelihood of secondary malignancies. Advances in radiation techniques, such as proton therapy, offer promising ways to reduce these risks by minimizing exposure to healthy tissues. Equally important is the role of vigilant, lifelong screening and follow-up care, particularly for survivors of pediatric and young adult cancers, as described in the aforementioned case of breast cancer following treatment for Hodgkin's Lymphoma in a young female. By integrating personalized treatment plans with survivorship care from the outset, healthcare providers can better protect patients while still delivering effective cancer treatment. As research progresses, the continued refinement of radiation therapy and heightened focus on survivorship will be essential in reducing the burden of secondary malignancies.

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