A review of radiation-related malignancy in the pelvis

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Abstract: Radiation therapy is a central treatment modality for the management of various pelvic malignancies and prior data has supported a relationship between radiation exposure and the development of long-term treatment sequelae. One of the most consequential long-term side effects of radiation therapy is the risk of developing a secondary malignancy. With advancements in radiotherapy delivery and a better appreciation of underlying tumor biology, additional considerations are needed when assessing the risk of radiation-mediated malignancies. Also, several adjacent normal structures within the pelvis may be affected by radiation-mediated toxicity, driven in part by acute and chronic inflammation. Depending on treatment modality and primary tumor location, various steps can be taken in radiation planning to reduce the risk of these side effects, which may negatively affect the patient's quality of life. As cancer survivorship continues to increase, it is important to understand both the treatment and biologic variables which influence the risk of developing secondary malignancies in order to minimize the risk for treatment side effects and the late effect of secondary malignancy. Herein, we will provide an overview of secondary malignancies in the context of receiving therapeutic radiation to the pelvis and will highlight biologic considerations that may influence this risk.

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Introduction

Rationale/background

An appreciable increase in cancer survivorship has been observed over the last several decades due to advancements in oncologic care. Concomitant with improved survival times, the probability of adverse treatment sequelae occurrence also increases. The development of a secondary malignant neoplasm (SMN) is one of the most consequential late effects following cancer treatment.

SMN is responsible for approximately 19% of the cancers diagnosed in the United States, which is secondary to the aging population and the increase in cancer survivors (1). Radiation therapy contributes to approximately 5% of these SMNs (2). Radiation therapy is the most commonly employed treatment modality in oncology, and given the larger percentage of cancer survivorship, it is important to consider the risk for SMN following radiotherapy. Prior data has established that radiation has carcinogenic potential (3), which has been underscored by the development of cancers in the survivors of the atomic bombs, Chernobyl accident and associated occupational exposures (4,5). In this context, radiation is mostly associated with the development of leukemia, thyroid, and breast cancers (6).

In contrast to the exposure of the spread of radioisotopes released into the atmosphere, targeted ionizing radiation

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directed at patient tissue represents an additional mechanism of radiation-induced malignancies. Clinical data on radiation-induced carcinogenesis in patients without prior malignancy or immunologic defects are rare. Prior data in patients treated for dermatologic, infectious or rheumatologic conditions with radiation have suggested increased risks of SMN in anatomic regions where the radiotherapy was directed (7-10). Data extrapolated from animal studies also support a risk for SMN development following radiation therapy. Combined data in over 100 canines exposed to intraoperative electron beam radiation have shown a significant latency period is required and that non-rapidly dividing tissues require higher cumulative radiation doses to induce a SMN (11,12). Edmondson *et al*. found 26% of mice developed a radiation-induced SMN, which was dependent on fractionation of radiation, total dose and genetic background (13). These tenets support the clinical rationale to minimize radiation exposure in younger patients, given the longer period of time to develop a SMN, and highlight the minimal consequence of SMN in older patients with anticipated poor survival outcomes.

One of the challenges in surveillance data, is attributing the development of SMNs in the context of other confounding variables, such as various environmental factors, like smoking, which have been associated with malignancy risk (6). Further, surveillance bias could confound results as patients are routinely asked about urinary and bowel symptoms following radiation to the pelvis, therefore warranting a deeper investigation as symptoms arise (14). Thus, in the setting of competing factors influencing risk of carcinogenesis, it is important to define criteria for radiation-induced SMN. In the 1940s, Cahan et al. first proposed criteria to define radiation-induced sarcomas (15). Later, Laskin *et al*. performed a pathologic assessment of radiation-induced sarcomas and noted most were poorly differentiated and suggested 3 criteria must be met to specify a radiation-induced SMN: (I) tumor must be in an anatomic site exposed to prior radiation, (II) tumor must be a different histology than the treated lesion, and (III) an appropriate duration of time must have elapsed between radiotherapy and SMN formation (16).

Of note, radiation-induced SMNs are usually described as an excess in risk over the estimated risk in the general population for a given tumor. Since radiation-mediated SMN is a relatively rare event, useful analyses must be performed in large study cohorts to identify statistically meaningful differences. For this reason, most studies evaluating radiation-induced SMN is confined to retrospective analyses on epidemiologic data. In order to best understand the impact of the studies included, it is important to consider the difference between absolute and relative risk (RR). Many of the included cohorts have data reported by RR, comparing two groups, one of which was treated by radiation. This is in contrast to the absolute risk, which relays risk over a period of time. Simply reporting RR conceals the absolute risk, which many times is more valuable to an individual patient (17). Risk assessment becomes more complicated when incorporating varying demographics, treatment approaches and polygenic traits, thus most models describe radiation-induced risk in the setting of RR. This distinction is paramount when counseling patients on radiation-induced SMN risk.

Objectives

In this review we provide an overview of the current literature related to radiation-mediated SMN risk in the context of age at exposure, temporality, solid versus hematologic malignancies, chemotherapy, radiation type, and genetic predisposition. Unless otherwise mentioned, radiation therapy refers to external beam radiation therapy.

Methods

Our search was conducted via PubMed with keywords that included “second primary cancer”, “subsequent neoplasm”, “radiation-induced malignancy”, “radiation malignancy”, and “childhood cancer survivorship”. Additional papers were found via the references from articles related to the original search.

Discussion

Radiation-mediated normal tissue injury

Although the exact mechanisms are unknown, radiation-induced normal tissue injury is a major contributor to treatment-related toxicity. Frequently, radiation oncologists are balancing this therapeutic ratio every day in clinic. The dogma of radiation-mediated cellular injury emphasizes damage to genetic material, which may be induced by double-stranded DNA breaks leading to compromised chromosomal integrity (18). By generation of free radicals and reactive oxygen species, radiation produces an

inflammatory response via various cytokine cascades. This inflammation poses a threat to adjacent normal tissue (19). The consequences of these effects are largely based on tissue diversity and their turnover (20). It is hypothesized that the response to injury and interaction between multiple cell types within an organ creates an ongoing process even after the treatment has been delivered (21).

Further detrimental synergy can occur when systemic therapies, which also disrupt cell cycle dynamics and induce further DNA damage, are added to radiation therapy. As both radiation and chemotherapy have been associated with SMN risk, this may create a "perfect storm" in the tissue microenvironment for subsequent SMN formation. These late combinatorial effects have been studied extensively in cardiac tissue with radiation therapy in combination with anthracycline-based chemotherapy regimens (22-24).

Within the pelvis, non-tumor tissues may undergo changes related to the mechanisms described above. The clinical consequences of normal tissue injury are partially dependent on whether the insulted tissue is organized in physiologic serial or parallel units. For example, nerves are considered serial structures as damage to any component can affect both upstream and downstream function. In contrast, a muscle group in the pelvis or a portion of the bladder has parallel units that may compensate if one portion of the tissue is damaged (25). This is important for consideration when assessing the consequences of radiation-mediated tissue effects.

The cell turnover characteristics of the tissue also contribute to the radiation response. We encourage further reading on this topic in the recent review by McBride *et al.* (20). For example, enteritis is acutely driven by endothelium injury and the cytotoxic effects on the crypt stem cells (26), whereas chronic enteritis is characterized by a more prolonged fibrotic process driven by fibrotic signaling pathways and telangiectasia formation (27). Similarly, cystitis also develops from a radiation-induced inflammatory process (28). Cystitis may be complicated by hemorrhage and clinical management is challenging (29). Analysis of peptides in the urine have demonstrated marker expression representing sequential fibrosis and vascular damage resulting in an inflammatory milieu in the bladder (30). Interestingly, acrolein, the byproduct of common chemotherapeutics (e.g., cyclophosphamide), induces robust inflammatory reactions when in contact with the bladder mucosa. This insult is perturbed with the co-administration of antioxidants (31). suggesting that the end result of both radiation or chemotherapeutic tissue damage culminates from uncontrolled inflammation.

The radiation-induced side effects, which are partially attributed to increased reactive oxygen species, may be dampened with the addition of amifostine. Amifostine is a thiol-containing molecule that scavenges free radicals, has additional protective pleiotropic effects, and appears to have selectivity for normal tissue (32). At present, amifostine is FDA approved to prevent xerostomia resulting from head and neck irradiation and in perturbing platinum chemotherapy-induced nephrotoxicity (33-35). Amifostine has also been shown in a randomized trial to reduce acute grade 2–3 toxicities in patients receiving pelvic radiotherapy for a variety of malignancies (36), which may be further improved with amifostine dose escalation (37). Though amifostine appears to decrease radiation-induced side effects to some degree, enthusiasm in the clinic has been tempered by patient intolerance, necessity for dosing right before radiation delivery and risk of hypotension. Whether amifostine decreases the risk of SMN is unknown.

Potential biologic mechanisms associated with SMN

The biologic mechanisms contributing to the development of SMN development are not known. Deleterious cellular effects of radiation have been attributed to induction of chromosomal aberrations and DNA damage in the context of diverse cell autonomous DNA repair capabilities and sustained non-lethal cell division events (38). SMN formation may also be influenced by tissue bystander effects, which are characterized by phenomena of genomic disruption and activation of signaling pathways in cells not directly exposed to radiation (39). Accumulating evidence also suggests non-irradiated cells can reduce the damage to irradiated cell populations through various soluble mediators (40). How these diverse processes influence radiation-induced SMN is a growing area of research.

Age at exposure

The risk of developing a SMN related to age at first radiation exposure has been well documented, which highlights those at younger ages have increased time to develop a SMN. Data from atomic bomb survivors has shown cancer risk is approximately 15% in those under 10 years of age at exposure, which decreases to 1% in those over 60 years old (41). Some studies have cited sensitivity to radiation as a primary mechanism when compared to adult populations (41). Broadly, cancer survivors treated with

radiation at an age above 18 years have a long-term risk of SMN across all body sites of 1.1 to 3 times higher than the general population (42), whereas risk in children are 5–10 times greater (43).

The Childhood Cancer Survivor Study (CCSS) followed 14,359 patients diagnosed between 1970 and 1986 under 21 years old and survived at least 5 years after initial diagnosis (44). Within this cohort, 10.5% received radiation only and about half received chemotherapy and radiation (45). At 30 years of follow-up, 20.5% (95% CI: 19.1–21.8%) developed a SMN, with those treated with radiation having a RR of 2.9 (95% CI: 2.1–4.2) (46). The average time to developing a SMN was 19±6.7 years with the average age being 29.5±9.1 years (45). Meningioma was the most common SMN with a RR of 16.6 (95% CI: 5.2–52.6) (45). When specific risk factors were analyzed, female survivors were at a greater risk for developing secondary malignancy than their male counterparts (RR: 1.46) (47). Breast cancer risk was generally increased in survivors who were treated with chest radiotherapy, but prior radiation to the pelvis was protective with a RR of 0.6 (95% CI: 0.4–0.9) (48). The CCSS cohort is limited in its data of site of radiation-induced SMNs; though, in children other groups have reported an increased risk of thyroid, central nervous system (CNS), and breast cancers (49). This data indicates the most common primary site related to radiation-mediated SMN varies by age, with most data relating to chest radiation and not to the pelvis.

Separate from therapy-related SMN risk, exposure from diagnostic radiology has been attributed with primary malignancy risk. In a study of individuals between 0–19 years and a median follow-up of 9.5 years, the cancer incidence was 24% higher in exposed *vs*. unexposed individuals; caveats to this data are the imaging eras (e.g., 1980s through 2000s) and how modern low-dose CT approaches in pediatrics now contribute (50). A study in Taiwan observed about a 3-fold increase in benign brain tumor, but not malignant tumor, identification in pediatrics exposed to CT scans of the head *vs*. those without exposure; this study was limited to lack of data on radiation dose, contribution of other diagnostic radiology exposures and baseline genetic predisposition (51). A similar study from the Netherlands also identified a small excess risk of malignant brain tumors following CT head imaging in the pediatric population. SMN of concern include leukemia, lymphoma, and CNS cancers (PMID, 26882064). Most studies have focused on CT head imaging, though it is possible that similar assertions can be applied to the pelvis as well. Though there is evidence for a small increased risk of tumor development in pediatrics exposed to radiation from diagnostic radiology, when clinically indicated, the benefit of CT imaging must outweigh the risk of concern for malignancy risk. In doing so, imaging in pediatrics with "as low as reasonably achievable" (ALARA) is a prudent approach to mitigate this risk.

Overall, though there appears to be an increased risk in children, detailed statistics on risk of SMNs related to radiation is limited because malignancy in children is relatively rare, and direct comparisons of SMN risk in anatomically similar tumors between pediatric and adult patients are not robust enough to make definitive conclusions.

Surveillance time to SMN

Surveillance time following cancer therapy varies based on parameters of the individual study and age at treatment. Two national cohorts have been paramount in the analysis of cancer related outcomes, the CCSS and the Surveillance, Epidemiology, and End Results (SEER) Program facilitated by the National Cancer Institute (52). For example, a SEER analysis of children who survived treatment of genitourinary malignancies found the peak risk of developing a SMN was 5 to 9 years after primary diagnosis and treatment (42).

Surveillance data centered in radiation-related malignancies is an additional consideration when choosing primary treatment strategy, especially when the primary diagnosis is at a young age. For example, in the PORTEC-1 trial at a median follow-up of 15 years, 22% and 16% of patients developed SMNs in radiation versus observation groups, respectively. Similarly, long-term surveillance of a cervical cancer cohort (n=107,706) treated with radiation identified an elevated risk of SMN, standardized incidence ratio (SIR) =1.3 (95% CI: 1.28–1.33) at a follow-up time of 40 years (53). Also, the risk of all SMN was higher in those treated with radiation therapy than those who were not, SIR =1.34 (95% CI: 1.31–1.38) and 1.06 (95% CI: 1.02–1.11), respectively (53). In another SEER analysis, the cumulative incidence of developing any SMN 25 years after radiation was 17.5% (95% CI: 17.1–17.9%) in uterine, 15.4% (95% CI: 14.0–16.8%) in vulvar, 13.2% (95% CI: 12.5–13.8%) in cervical, and 9.4% (95% CI: 8.9–9.9%) in ovarian cancers (42). As surveillance time lengthens, the chance for developing SMN increases in most cases, however, it is important to consider the confounding risks that are given additional time to develop as well.

Table 1 Radiation-related pelvic malignancies

Primary tumor site treated with radiotherapy	No. of patients	Site of secondary malignant neoplasm	Site of secondary malignant neoplasm	Patient follow-up time (years)	Reference #
Prostate	122,123	RR: 15% & 34%	Bladder, rectum, colon	5 & 10	(54)
	397,416	RR: 1.30 (95% CI, 1.19–1.42)	Bladder	5	(55)
	242,878	RR: 1.94 (95% CI, 1.07–3.50)	Rectum	5	(55)
	34,889	RR: 1.5 (95% CI, 1.1–2.0)	Bladder	5	(56)
	192,658	SHR: 1.89 (95% CI: 1.66–2.16)		Median: 6 (0–24)	(57)
Bladder	192,658	SHR: 0.67 (95% CI 0.47–0.94)		Median: 6 (0–24)	(57)
Rectal	1,599	RR: 1.85 (95% CI 1.23–2.78)	Adjacent to rectum	20	(58)
	2,554	No SMN risk		Median: 13 (1.8–21.2)	(59)
Gynecologic	568	RR: 2.02 (95% CI, 1.30–3.15)	Not specified	20.5	(60)
	60,949	RR: 1.26 (95% CI, 1.16–1.36)	Solid tumor malignancies	30	(61)
	199,268	HR: 1.72 (95% CI, 1.37–2.15)	Leukemia	5–15	(62)
	192,658	RR: 1.5 (95% CI, 1.13–2.00)	Rectum	Median: 6 (0–24)	(57)
Cervical	104,760	RR: 1.30 (95% CI, 1.28–1.33)	Colon, rectum/anus, urinary bladder, ovary, and genital sites	40	(53)
	182,040	RR: 1.1	Bladder, rectum, uterine corpus, ovary, small intestine, bone, and connective tissue	>1	(63)

HR, hazard ratio; RR, relative risk; SHR, sub-hazard ratio; SMN, secondary malignant neoplasm.

Specific pelvic tumor types

It is difficult to accurately define the risk of SMN induced by radiation because most studies do not have an appropriate non-irradiated control group. Some tumors in the pelvis are effectively managed by surgery or radiation, therefore this provides opportunity to have a case and control group for comparisons. Prostate, bladder, rectal, and gynecological (e.g., endometrial, cervical) carcinomas will be discussed with their significance related to development of SMN (*Table 1*).

Prostate cancer

Localized prostate cancer is treated definitively with radical prostatectomy or radiation therapy, which are curative in most instances (64). Several studies have demonstrated prostate cancer patients treated with radiation have an increased risk of developing SMNs, particularly in organs within close proximity to the treated prostate, such as the bladder, rectum, and colon (14,54,55,65,66). Incidence data from the SEER cancer registry compared 51,584 men with prostate cancer who were treated with radiation or surgery without radiation. In this study, radiation therapy was associated with a 6% increase in risk of solid SMN, with this reaching 15% and 34% at 5 and 10 years of follow-up, respectively (54). Similarly, a study in 39,028 men found that at a median follow-up of 5 years, 7.4% of men developed a SMN, which persisted after adjustment of other treatment and clinical confounders (67). An earlier cohort (n=34,889) analysis found a RR of 1.3 (95% CI: 1.0–1.7) for developing bladder cancer at 5 years after radiation compared to those not treated with radiotherapy; interestingly this increased risk peaked at 8 years (RR =1.5; 95% CI: 1.1–2.0) (56). Rombouts *et al*. also found a significantly increased risk (HR =1.89, 95% CI: 1.66–2.16) for developing a secondary rectal cancer in men treated with radiation for prostate cancer (57), yet no significant risk

was reported for hematologic cancers (54,55). With longer surveillance, the odds of developing bladder or rectal cancer after radiotherapy *vs*. surgery were 1.3 *vs*. 1.9 at 5 years and 1.7 *vs*. 2.2 at 10 years, respectively (55). In contrast, Curtis *et al*. found patients treated with prostate radiation had an increased risk of developing bladder cancer, but no increase in rectal cancer (42). Similarly, Kendal *et al*. also observed no increase in rectal cancers in men treated with prostate radiation after adjusting for confounders (68).

Chrouser *et al*. found an excess of bladder cancer cases in men treated with prostate bed radiation only (69), whereas a study in the British Columbia Tumor Registry found no excess of risk in irradiated patients over a non-irradiated cohort (66). In a single institution report, Liauw *et al*. found patients treated with brachytherapy alone had a lower incidence of bladder and colorectal SMNs compared to brachytherapy with supplemental radiation (70). Also, Wang *et al*. performed a SEER analysis on men treated with radiotherapy, brachytherapy, or prostatectomy and found that both radiotherapy and brachytherapy were associated with an increased risk of SMN compared to surgery, though the absolute increase was 1% after 10 years (71). Also, patients treated with prostatectomy were half as likely to have post-treatment bladder cancer compared to patients who underwent radiation therapy (HR =2.08, 95% CI: 0.29–3.9) (72). Keehn *et al*. found all radiation modalities increased the risk of bladder cancer, but prostate brachytherapy was associated with the largest increase after 10 years (73). To complicate these observations further, prior data suggests the rate of bladder cancer in patients with prostate cancer is 18 times higher than expected, even in the absence of radiation treatment (74), and that simultaneous diagnosis of both cancers occurs between 0.4–6.6% of the time (75). Overall, there should be some caution in concluding prostate or prostate bed radiation definitively elevates rectal and bladder cancer incidence, as the risk is low, there are competing risks and the data to infer risk are incomplete and conflicting.

Rectal cancer

Treating rectal cancer with radiation therapy carries a risk for structural changes to the bowel wall. Patients may suffer from rectal wall toxicity secondary to an inflammation (i.e., proctitis) and fibrosis sequence, which can manifest as tenesmus, changes in bowel habits and rectal bleeding. Most patients have self-limiting effects during treatment, which resolve with conservative therapy and surveillance. Dose-volume relationships have been evaluated in several settings of pelvic radiation, which includes conventional and hypofractionated approaches (76). From these investigations, "generalized" dose constraints from the population have been employed in radiation planning to minimize rectal toxicity risk. With modern advancements in conformal and inverse-planning radiation delivery, proctitis is significantly lower (77). Chronic proctitis is seen in about 5% of patients and can be complicated by fistula formation, bowel obstruction and permanent changes to bowel habits (78). A systematic review of 21 studies evaluating rectal and anal function following prostate radiation found that radiation may reduce anal resting pressure, decrease compliance of the rectum and induce telangiectasias formation (79). Whether this initial inflammatory cascade induced by radiation predisposes surrounding normal rectal mucosa to malignancy is unknown. A recent study evaluating non-neoplastic rectal mucosa after preoperative rectal radiation noted histologic findings of dysplasia, but next generation sequencing demonstrated no increased risk of genetic aberrations (80). This should be interpreted in the context of tissue analysis immediately following radiation *vs*. the risk of genetic changes that may occur over several years.

Primary rectal cancer treatment with radiation has also been associated with increased risk for SMN. According to a SEER-based analysis of 77,436 patients followed with primary cancer at the rectosigmoid junction, 28% received a form of radiation therapy in their treatment. Of the patients who received radiation therapy, 7.7% developed a SMN, with 26% being within the digestive tract and 15% specifically within the colon. In the same study, 63% of anal cancer patients were treated with radiation and 10.3% developed a SMN, with no specification for SMN location after radiation (42). Birgisson *et al*. also found an elevated risk (RR =2.04, 95% CI: 0.97–3.27) of SMN in patients treated with rectal radiation in the Uppsala and Swedish Rectal Cancer Trial, with most instances being in tissue adjacent to the irradiated volume (58). In contrast, Wiltink *et al*. found no increase in SMN risk in a pooled analysis of >2,500 trial patients treated with or without radiation for pelvic malignancies; they did find that patients with rectal or endometrial primary cancers had increased probability to develop secondary cancers compared to the general population (59). Kendal and Nicholas also found in a population-based analysis that secondary cancers after irradiation for rectal cancers are infrequent and should not be factored into treatment decisions when assessing risk in an older population of patients (81). A modeling study by Zwahlen *et al*. found that rectal radiation can increase

SMN risk by 2% in older patients, but may increase the risk up to 10% in those less than 30 years of age (82). Overall, the data regarding radiation-induced rectal cancer is also conflicting, but there may be some increased risk compared to not treatment not employing radiotherapy.

Gynecologic cancers

Additional solid tumor malignancies are particularly common in patients with endometrial cancer and several studies have examined the risk of SMN following radiation treatment for this disease. A SEER analysis of patients treated with radiation for uterine cancer who survived at least one year were found to have increased risk for SMN compared to patients who had received surgery alone. In this study, combined radiation and brachytherapy had the strongest association with new solid malignancies in the cohort of patients who developed SMN (61). Additionally, external bream radiotherapy has been associated with an increased risk for SMN, especially in women treated before the age of 60 (HR =2.02, 95% CI: 1.30–3.15) (60).

Women treated for cervical cancer at a younger age sustain a significantly higher risk for SMN due to radiation (53,62). Consistent risk factors among cervical cancer survivors include exposure to radiation, human papillomavirus, and smoking, which are associated with a 40-year cumulative risk of any SMN of 22% (53). It is unclear whether risk factors in cervical cancer are synergistic as in lung cancer, where radiotherapy and smoking have shown increased risk for developing Hodgkin lymphoma (53). In a cohort study of cervical cancer survivors (n=104,760), radiation was a significant risk factor for developing a SMN at any site, as well as locally at sites receiving greater than 3 Gy (53). Interestingly, a reduction in the risk of breast cancer was observed after pelvic radiation, which could be attributed to age of treatment or a change in hormone exposure to breast tissue after hysterectomy and ovarian ablation (53,83). This is underscored by a study demonstrating that more than 6 Gy to the ovaries reduced breast cancer risk by 44% (84).

Hematologic malignancies

Radiation has been associated with an increased risk for developing various hematologic malignancies, such as acute myelogenous leukemia, chronic myelogenous leukemia, and acute lymphoblastic leukemia (6). In contrast, chronic lymphocytic leukemia has not been associated with radiation (6,63,85). The risk for non-lymphocytic leukemia was significant in the first decade of follow-up (SIR =2.74), whereas risk for chronic lymphocytic leukemia was not significantly increased any time after radiation exposure (53,63). Thus, for those patients who are susceptible to developing leukemia following radiation, the time is usually a few years compared to >10 years for the development of most solid tumors (84,86). Single, large doses of radiation are more associated with development of leukemia, as opposed to small doses over a lifetime (87). Further, at low doses (<1 Gy), the predicted leukemia excess RR increases linearly with dose (86).

It is estimated that more than 40% of active bone marrow mass is contained within the pelvic region, which may contribute to the risk of developing leukemias after pelvic radiation therapy (88). More recent estimates have confirmed that the pelvic bones (17.5%), sacrum (9.9%), L5 vertebra (2.5%) are responsible for a large fraction of active bone marrow in adults (86). Due to the enrichment of calcium, the absorbed dose in bone can be much greater than surrounding soft tissue (89). Radiation has been shown to change the bone microenvironment, which may be characterized by altered osteo-clast-blast balance and replacement of marrow with adipose tissue (90). How these altered bone environments may contribute to SMN risk is unknown. It is possible bone marrow stem cells exposed to radiation may acquire genetic abnormalities or that depletion of certain marrow compartments may lead to decreased immune cell surveillance in the host. Understanding the consequences and mechanisms of bone marrow irradiation and SMN risk is an area of needed investigation.

Depending on the treatment scenario, conformal radiation may be planned to spare dose to the bone marrow in the pelvis. Advanced conformal radiation delivery techniques employing intensity-modulated radiation therapy (IMRT) can reduce the volume of pelvic bone marrow receiving a specified radiation dose. This reduction of bone marrow dose has been shown to reduce acute grade ≥3 hematologic toxicity in patients receiving pelvic radiation and concurrent chemotherapy by approximately 10% (91). Further refinement of this IMRT approach with ^{18}F-fluorodeoxyglucose positron emission tomography (PET) delineation of active bone marrow has been shown to be feasible (92,93) and is currently being employed in clinical trial development.

In a large study (n=199,268) of patients treated with pelvic radiation for tumors of the vulva, cervix, uterus, anus, and rectosigmoid junction, just over one-third of

patients who received radiation had a 72% increased RR for developing a secondary leukemia. This risk peaked at 5 to 10 years after treatment (HR =1.82, 95% CI: 1.40–2.44) and remained elevated at 15 years of follow-up (HR =1.5, 95% CI: 1.03–2.18); interestingly, there was no significant risk for multiple myeloma (62). Some studies have also found that cervical cancer patients may have an increased risk for leukemia, and treatment with radiation seems to increase this risk further (53). Similar findings have identified an association in the treatment of testicular cancer, citing a greater total volume of bone marrow exposed to radiation is associated with an 11-fold risk of leukemia (6,94,95). At 5 years of follow-up after prostate radiation, Journy *et al*. found less than 1% of patients developed a leukemia or myelodysplasia (67) and Wang *et al*. also found an absolute risk increase of 0.5% for hematologic malignancies after prostate radiation at 10 years of follow-up (71).

Chemotherapy risk

A potential confounding variable to consider when examining risk of radiation-mediated malignancy is the use of cytotoxic chemotherapy, which is frequently delivered in combination or in sequence with radiation. The leukemogenic potential of chemotherapy is well established, where the RR of leukemia after radiation is considerably smaller than after chemotherapy alone to the order of approximately 2-fold (6). In a study of ovarian cancer patients (n=28,791), the risk of SMN was differential based on the class of chemotherapy, where the overall risk of leukemia following platinum-based therapy was 4.0 (95% CI: 1.4–11.4) (96). Patients who had received platinum-based chemotherapy in addition to radiation were found to have significantly higher risk of leukemia when compared to platinum-based chemotherapy alone, suggesting different chemotherapies synergize with radiation to induce leukemias (6,96). Also, analysis of the CCSS cohort found 49% of participants received chemotherapy and radiation, 10.5% received radiation alone, and 21.5% received chemotherapy alone. Of these, 61% developed a subsequent neoplasm when treated with both chemotherapy and radiation, compared to 8% and 20% treated with radiation or chemotherapy alone, respectively (45).

Radiation modality and associated risk

Assessment of SMN risk related to radiation approach requires data on patients treated with different radiation modalities with extended follow-up in order to identify the event; unfortunately, such data is currently limited. A general dose-response relationship leading to development of SMN has been documented in both adult and pediatric populations (97,98). Specifically, these studies demonstrated there may be a threshold of the integral radiation dose that non-tumor tissue can be exposed to before a delayed SMN occurs.

Various approaches are employed to deliver tumoricidal radiation doses to patients with the goal to spare normal tissues as much as possible. Though many efforts are made to spare healthy normal tissue from radiation, the dose interface between tumor and normal tissue is never zero. This is a consequence of scattered radiation within the patient, beam-limiting devices, dose leakage and the production of secondary radiation (99). As technology has advanced, radiation delivery now encompasses two-dimensional targeting, three-dimensional conformal radiotherapy (3DCRT), IMRT and particle therapy, such as proton beam therapy (PBT).

Previously, investigators postulated IMRT may increase SMN risk due to greater normal tissue volumes receiving low-dose radiation, which is intrinsic to IMRT dose distribution (100). Though IMRT reduces radiation dose to the bladder, rectum and femoral heads compared to 3DCRT, Tao *et al*. found IMRT increases the volume of non-tumor tissue in the pelvis receiving 5–30 Gy and raises the mean radiation dose outside the pelvis by approximately 7% (101). Diallo *et al*. analyzed the dosimetric data of 115 young patients who developed SMNs and found that only 12% of SMNs arose within the high dose irradiated volume. Further, they observed two-thirds of SMNs arose in the region <5 cm from the beam border (102). Though this data is not specific to pelvic malignancies, it does highlight the risk of organs in close proximity to targets like the prostate, bladder, rectum and nodal fields, which may receive an intermediate radiation dose. Modeling studies on dose have suggested carcinoma SMN risk decreases by 10% and sarcoma SMN risk decreases by 15% per 1 Gy increase per fraction; this suggests that shorter courses of radiation with higher doses per fraction may decrease SMN risk (103). Thus, in some instances radiation dose distribution can increase SMN risk, but the manner in which the cumulative dose is delivered may counter this risk.

Treatment with PBT can reduce the total integral radiation dose because protons deposit most of their energy at a specified depth (e.g., Bragg peak) with little exit dose (104). Chung *et al*. found that compared to photon

therapy, PBT reduces SMN formation by approximately 2%, which remained significant after adjustment for other clinical factors (105). Schneider *et al*. suggested spot-scanning PBT reduces the risk of SMN formation compared to IMRT and this was supported by a study by Fontenot *et al*. who also found PBT reduces the risk of SMN by 26% to 39% depending on patient body habitus (106). In the context of young children and adolescents, PBT may decrease the risk of SMN and is a major reason why this modality is employed in pediatric malignancies (107).

A recent SEER-Medicare analysis of men treated for prostate cancer found no difference in the overall SMN RR between 3DCRT and IMRT; though, there was preliminary data supporting a reduction in rectal and colon cancer with IMRT, but not bladder cancer (67). Most recently, a National Cancer Database study evaluated SMN risk relative to radiation treatment modality in over 450,000 patients spanning 9 tumor types across various anatomic locations. This study found at a median 5 years of follow-up, the absolute risk of SMN was 1.55/100 patient-years with no differences observed between 3DCRT and IMRT; though, patients treated with PBT had a lower odds (OR =0.31, 95% CI: 0.26–0.36) of developing a SMN compared to IMRT (108). Thus, this data implies there may be advantages to using PBT to reduce secondary malignancy risk compared to other modalities, though with caveats of limited follow-up, incomplete demographics, and genetic predispositions.

Genetic predisposition and risk

Prior data indicates that beyond 10 years, about 9% of cancer survivors develop a SMN, with an estimated 0.5% excess absolute risk at 15 years attributed to radiation therapy (109). Several physical and treatment parameters have implied children are at increased risk of SMNs compared to adults when exposed to radiation. Another factor that may also contribute to increased SMN risk is the underlying genetics of each patient. Whereas many adults develop cancer in the setting of perpetual genomic insults secondary to lifestyle choices or occupational exposures, many children develop cancers due to germline mutations (99). This begs the question of whether intrinsic genetic susceptibilities influence radiation-related risk of SMN development. With the advent and increasing implementation of genetic profiling in cancer patients, more data in this venue is likely to improve our understanding.

Within a patient, the reaction to radiation appears to be mostly ascribed to patient-specific characteristics (110). The general population is assumed to have a uniform sensitivity to radiation, though several rare syndromes have been identified that increase radiation sensitivity and appear to be associated with single genetic aberrations (111). Several "pathogenic" gene variants have been identified which confer an increased risk of cancer development and possibly toxicity to radiation therapy. For instance, patients with alterations in the *BRCA1* or *BRCA2* genes have an increased risk of developing contralateral secondary breast primary tumors in the absence of radiation (112) or those with bilateral retinoblastomas driven by *RB1* aberrations have increased risk of radiation-induced osteosarcomas (113). Although *BRCA* carriers have an enhanced risk for malignancy, no increased risk of radiation-induced SMN formation has been identified (114). The lack of an increased SMN incidence after radiation in carriers suggests other variables other than maintenance of DNA fidelity contribute to this process. In contrast, patients with *TP53* alterations resulting in Li-Fraumeni syndrome have been estimated to have approximately >20% excess risk for radiation-induced SMN (115). A study including prostate cancer patients identified a single nucleotide polymorphism (SNP) in *ATM*, which increased the risk for acute toxicity, but whether this is related to SMN is unknown (116). Other SNP studies in prostate cancer have found alterations in *TANC1* (117), *KDM3B* and *DNAH5* (118) are associated with toxicity to normal organs in the pelvis following radiation. Again, whether this corresponds to SMN risk is unknown. It is also important to appreciate that the majority of somatic mutations in tumors are likely not present in normal tissues, thus relating certain mutations to normal tissue risk of SMN remains unclear.

Summary

The development of SMNs is a significant late sequelae risk following radiotherapy. In general, cancer survivors who were treated with radiation have increased risk to develop SMNs compared to the general public. This risk is determined by age at exposure, radiation dose, volume of irradiated normal tissue, biologic parameters and adequate follow-up time to identify the event. Importantly, most data supporting increased risk for radiation-induced SMNs is based on retrospective epidemiologic data, dose-response models from homogenous exposures of radioisotopes in the atmosphere, and with little consideration of patient-specific biologic predisposition. As the cancer care continuum

continues to advance and patient survival improves, understanding the complexities of what drives SMN risk is of utmost importance.

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