

Review Article

Radiation Induced Second Malignancies (RISM): Risk, Diagnosis, Treatments and Review of Literature

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Abstract:

Information concerning radiation-induced malignancies comes from the A-bomb survivors and from medically exposed individuals, including second malignancies in radiation therapy patients. The A-bomb survivors show an excess incidence of carcinomas in tissues such as the gastrointestinal tract, breast, thyroid, and bladder, which is linear with dose up to about 2.5 Sv. There is great uncertainty concerning the dose-response relationship for radiation-induced carcinogenesis at higher doses. Some animal and human data suggest a decrease at higher doses, usually attributed to cell killing; other data suggest a plateau in dose. Modern treatment modalities such as passive proton therapy and intensity modulated radiation therapy (IMRT) produce large amounts of scatter, leakage and neutron radiation, which has been found to be directly proportional to the risk of second malignancy incidence. Organs closer to the target typically receive higher and less homogeneous doses of cell killing and repopulation effects play an increasing role. The most common type of cancer caused by radiation is sarcoma, which is typically a cancer of muscle, bone, or blood vessel origin. We reviewed the literature with key words "Radiation induced second malignancies, second primary tumour, second cancer" to find relevant articles describing risk, diagnosis and treatments of radiation induced second malignancies.

Key words: Radiation, Second malignancy, Second primary cancer, Second cancer;

Introduction:

It may be difficult to distinguish between radiation-induced cancers, late recurrences after radiation and second primary tumors that develop despite radiation. The definition of a radiation-induced cancer was established by Cahan in 1948 and specifies that a radiation induced cancer must occur within the treatment field, have a significant latency and be a different kind of cancer than the original type¹.

The high frequency of second primary cancers appearing in patients with squamous cell carcinoma of the head and neck confounds analysis in this region largely due to field cancerization, often of a similar type. Although higher rates have been reported in the past, a study from 1999 identified second malignancies to develop at a rate of 2.3% per year in the respiratory and upper tracts of 1609 patients with early stage squamous cell carcinoma of the head and neck².

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The risk of developing a second cancer for head and neck cancer patients treated surgically was 2.2/1000 person per year compared to 2.9/1000 person per year among those treated with radiation. The risk of a second cancer has been shown to increase with time and radiation dose with the latency before appearance of a second cancer differing between organs. The risk of cancer of the rectum and bladder starts to increase 10 years after exposure, whereas leukaemia develops within 2-3 years after exposure with a peak at 5 to 6 years³.

Radiation induced Risk of Second Malignancies:

Risk of breast cancer after chest irradiation

Whole-lung irradiation confers greater risk of breast cancer than previously recognized⁴. In women with a history of radiotherapy (RT) for Hodgkin's Lymphoma (HL), breast cancer is diagnosed at an earlier stage, but these women are at greater risk for bilateral disease and are also at increased risk of metachronous contralateral breast cancer⁵. For developing breast cancer as 2nd malignancy, 136-fold increase for girls who received RT before the age of 15 years and no increased risk for women treated after age 30⁶.

Risk of 2nd cancer after breast irradiation

Breast cancer patients experience a small but significant risk of developing second non-breast cancer after radiotherapy treatment⁷ {Young patients (<50) higher lung cancer; older patients (>50) higher soft tissue sarcoma (STS)}. RT associated with increased risk of sarcoma, but magnitude of risk is small. Angiosarcoma has significantly more prevalent⁸ (15-year sarcoma incidence RT 0.3% vs. no RT 0.2%). Following radiation treatment of breast cancer, RT is associated with higher risk of developing sarcoma⁹.

Risk of 2nd primary cancer after pelvic irradiation

Risk of second cancers after radiotherapy for cervical cancer is small but significant; benefit of RT outweighs the risk¹⁰ {2nd cancers (1%), 1.6% excess risk per person per decade, cumulative risk 24% at 30 years}. In case of testicular cancer, RT and chemotherapy increase risk of second malignancies (SMN) {second malignancies (10%), risk 1.7x over general population and SMN by modality: sub-diaphragmatic RT 2.6x, chemo 2.1 x over surgery alone}¹¹. For patients diagnosed at age 35 years, cumulative risks of solid cancer to age 75 years were 36% (seminoma) and 31% (nonseminomas), compared with 23% for the general population¹².

Risk of 2nd malignancies after radiation (other site) therapy

Risk of second cancer (SC) associated with younger age at HD diagnosis, largest risk for breast, other supradiaphragmatic sites, infradiaphragmatic, malignant mesothelioma¹³ {30 yr risk for solid cancer 18% (men) / 26%(women) for patients diagnosed at age 30, vs 7% / 9% general population}. In Ewing's sarcoma, overall risk of 2nd malignancies similar to other pediatric tumors¹⁴ (20-year cumulative incidence: 9.2% for any malignancy, 6.5% for sarcoma, dose-response: none in <48 Gy, 130/10,000 for >60 Gy). Neurofibromatosis 1(NF1) patients with optic glioma (OPG) treated with RT alone or in combination (Dose 25-50 Gy), significantly increased 2nd CNS cancer risk in NF1 patients with OPG¹⁵. Childhood cancer survivors has substantial and increasing risk for second neoplasms¹⁶ (Second malignancy rate 6%, 30-year cumulative incidence of SMN 9%, nonmelanoma skin cancer 7%, risk elevated after >20 years and risks differs by subtype).

Diagnosis:

Imaging

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are the imaging modalities of choice to evaluate and follow or to look for distant spread of the disease. Imaging features are not pathognomonic

and can be difficult to interpret. It can be very difficult to exclude a recurrence of the primary tumor when relying on imaging alone¹⁷.

Pathological findings

Core needle biopsy is mandatory in confirming the diagnosis. The biopsy will distinguish between a new malignancy, recurrence of the primary malignancy, and post-operative or post-radiotherapy changes. Biopsy will also indicate the histologic subtype and grade of the disease.

Molecular biology

Very little is known about the genetic changes involved in the tumorigenesis of postirradiation sarcomas. According to a recent study and review by Mertens et al regarding cytogenetic changes in Radiation Induced Sarcoma (RIS), these tumors have complex karyotypes, with loss of 3p21-pter being more frequent than in sporadic sarcomas. Also, polyclonal tumors with near-diploid chromosome numbers (few or no karyotypic abnormalities) were observed¹⁸.

Treatments:

Surgery

Radical resection with negative histological margins (R0) is the treatment of choice for localized disease. Surgical resection includes wide excision, limb-sparing surgery or forequarter amputation etc. Previous irradiation impairs anatomic and tumor planes, preventing surgeons from appreciating true tumor margins. This further reinforces the necessity for aggressive and wide resection, especially considering that a positive surgical margin will reduce survival by nearly half⁹.

Major plastic surgical reconstruction can be required, ranging from split thickness skin grafting to local flaps and free tissue transfer. Sometimes it is necessary to reconstruct the chest or abdominal wall using a polypropylene mesh and methyl methacrylate sandwich technique^{20,21}. Due to the high incidence of multifocal RIS after breast cancer treatment, in particular breast angiosarcoma post-radiation and breast-conserving therapy (BAPBCT), a surgeon might consider removing the entire irradiated area and not just the tumor²².

Radiation therapy

Additional radiation therapy using modern techniques may be considered²³, but there are concerns about toxicity, as repeated high-dose radiotherapy is often impossible due to limited bone marrow function. Data from case reports have been published on hyperfractionated radiotherapy for BAPBCT¹¹ showing

certain efficacy. BAPBCT tumors have a high growth rate, making them more likely to repopulate between daily fractions of radiotherapy. The use of multiple daily fractions might, therefore, prevent repopulation from occurring²⁴.

Chemotherapy

For metastatic disease, palliative chemotherapy is the treatment of choice for the majority of the diseases and anti-angiogenic drugs, such as sorafenib and sunitinib, have shown some efficiency in angiosarcomas²⁵.

Chemotherapy can be administered in the neoadjuvant setting, before surgical resection, to improve local control and eradicate subclinical metastatic disease.

Conclusion:

Since the majority of cancer patients receive radiotherapy, it is critical that clinicians are aware of the potential development of radiation induced 2nd malignancy, which can occur decades after radiotherapy. Any abnormality should be biopsied, and if a cancer is detected, the treatment of choice is surgical resection with negative margins. Future studies analyzing clinical and pathological characteristics of primary tumors, and breast cancers in particular, can help to identify factors that predispose to Radiation Induced Second Malignancies (RISM) for better selection of patients undergoing radiotherapy. Another issue is to examine the genetics of RISM, which may illuminate the mechanisms responsible for carcinogenesis.

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