Radiation-Induced Malignancies Making Radiotherapy a “Two-Edged Sword”: A Review of Literature

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Abstract

Radiotherapy is one of the modalities of treatment of malignancies. Radiation-induced malignancies (RIMs) are late complications of radiotherapy, seen among the survivors of both adult and pediatric cancers. Mutagenesis of normal tissues is the basis for RIMs. The aim of this review of literature was to discuss epidemiology, factors affecting and different settings in which RIM occur.

Keywords: Radiation-induced malignancies; Late side effect; Mutations

Introduction

In medical field, radiation is being commonly used in diagnostic radiology and as therapeutic modality for various malignant as well as non-malignant diseases. During the last few decades, use of radiation has been extensively increased for commercial purposes, e.g. nuclear power plants, disinfectants, agriculture (food preservation and pest control) and others.

One of the worst consequences of radiation exposure is radiation-induced malignancy (RIM). Although the pathogenesis is not well defined, mutation of normal tissues by radiation-induced injury may be the possible mechanism.

Patients cured of primary malignancy have chances of development of various other malignancies (secondary). Radiotherapy may cause mutagenesis in normal tissue and lead to RIM. There are several characteristic features of RIM.

Definition

Cahan’s criteria were given by Cahan et al \cite{1} in 1948, which were used to define a radiation-induced sarcoma. They are currently being used as the standard for demonstration of RIM.

The modified Cahan’s criteria for diagnosis of RIM are as follows. a) A RIM must have arisen in an irradiated field. b) A sufficient latent period, preferably longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy. c) The treated tumor and alleged induced tumor must have been biopsied. The two tumors must be of different histology. d) The tissue in which the alleged induced tumor arose must have been normal (i.e., metabolically and genetically normal) prior to the radiation exposure.

Atom bomb survivors

Concept of radiation-induced cancer comes from survivors of the atom bomb attacks on Japan. There are two types of radiation emitted from bomb: initial directly emitted radiation and residual radiation. The residual radiations are of two types. First is radiation emitted from induced radioisotopes in soil and metal and second is the nuclear fission products \cite{2}.

A number of leukemia cases were noticed in the first few years with peak at 6 - 8 years after the bombings and the relative risk (RR) among children exposed at the age of 10 years was approximately more than 70 times. It is clear that the risk of solid malignancies (bladder, female breast, lung, brain, thyroid gland, colon, esophagus, ovary, stomach, liver and skin (excluding melanoma)) has also increased after the bombing and even persists today \cite{2}. Hall concluded the overall risk of fatal cancers in atom bomb survivors to be 8%/Gy \cite{3}.

Histology

Radiotherapy can induce a wide variety of histologic types of malignancy, which cannot be distinguished from natural occurring tumor. In future molecular forensics may have a role in their diagnosis \cite{4, 5}. Carcinoma and leukemias are commonly seen in organs receiving low dose radiation and at regions distant from the treatment site; whereas sarcomas are predominantly seen arising in tissues or organ receiving high dose radiation in or close to the radiation fields \cite{3}.

Dose and linear energy transfer (LET)

RIMs are more common with high LET radiation (alpha parti-
Radiation Induced Malignancies in Radiotherapy

icles and neutrons) doses than with low LET (X-rays and gamma rays) doses, especially at low dose rates [6]. The relative biological effectiveness (RBE) for malignant transformation and cytotoxicity increases with increasing LET of the radiation [7].

Energy

RIMs are commonly seen with orthovoltage in comparison to megavoltage radiotherapy. It has been proposed that bone receives a higher dose with orthovoltage radiotherapy and patients receiving this survive longer and thus have higher chance of getting RIM [8].

Age

RIMs are common in children in comparison to adults. It is said that genotoxic injury to the stem cells and longer survival in childhood malignancies may be the reasons behind this phenomenon [9].

Other factors

Factors including chemotherapy, environmental exposure and hereditary predisposition (familial retinoblastoma, tuberous sclerosis, and neurofibromatosis I) can increase the risk of cancer development after radiation exposure [10, 11].

Pathogenesis of RIM

The molecular processes involved in increasing susceptibility and development of RIM are not well understood. Genetic alterations and genomic injury are proposed mechanisms for radiation-induced tumorigenesis in normal tissues. According to Best et al, genome wide association studies (GWASs) have earned some success in identifying significant predictors of cancer susceptibility in cancer survivors [12].

The bystander effect is a phenomenon, which is observed after radiation and chemical exposure, in which the untreated cells demonstrate abnormalities mimicking exposure, such as chromosomal instability, after irradiation [13]. It may be the mechanism of RIM in non-targeted tissues [14].

RIMs After Radiotherapy in Non-Oncological and Oncological Conditions

There are various reports in literature, which show evidence of RIM after radiotherapy of primary disease (non-oncological and oncological).

RIM after head and neck irradiation

Earlier various rheumatologic, infectious and dermatological conditions were treated with low dose radiotherapy which after years led to solid and hematological malignancies (Table 1) [15-18].

Because of longer survival of these patients, they get an adequate latency period to develop RIM in contrast to malignant disorders. In view of this late and adverse side effect, radiotherapy is no longer recommended for the management of non-oncological disease.

RIM after thoracic irradiation

In both definitive and adjuvant settings, radiotherapy is commonly used to treat head and neck carcinoma. The most common histologic sub-types as RIM are squamous cell carcinoma followed by soft tissue sarcoma. In 1989, a study by Cooper et al showed 110 second, independent, malignant tumors out of 928 patients with squamous cell carcinoma of head and neck [19]. Toda et al investigated 322 patients in a retrospective study who had received radiotherapy for early-stage non-Hodgkin’s lymphoma (NHL) of the head and neck and found four cases of RIM [20].

RIM after thoracic irradiation

Breast cancer is one of the most common malignancies in females worldwide. Radiotherapy is included in the treatment
depending upon the stage and histopathological findings. Carcinomas involving lung, contralateral breast, esophagus and sarcoma are the RIMs associated with breast cancer radiotherapy (Table 2) [21-24].

Travis et al concluded that hormonal status is important for radiation-induced breast cancer as ovarian ablation either by radiotherapy or chemotherapy can decrease its incidence [25].

Radiotherapy has a role in the treatment of Hodgkin disease (HD) in case of bulky and residual disease. Decades ago, classic mantle field was designed to treat several nodal stations commonly involved in HD. This broad nodal irradiation causes multiple late toxicities including RIM. Patients surviving HD are considered at higher risk of development of radiation-induced breast, lung and thyroid cancers [26-28].

According to Travis et al, radiation-induced breast cancer after radiotherapy and chemotherapy given for HD depends on the dose of radiotherapy (risk increases with dose), age (common in younger females) and chemotherapy (risk decreases with increasing numbers of alkylating agent cycles) [25].

### RIM after pelvic or genitourinary irradiation

RIMs have been reported after pelvic irradiation for cervix, endometrium, prostate and testis (Table 3) [29-32].

### RIM after radiotherapy for leukemia

Radiotherapy is used in the treatment of leukemia in the form of prophylactic craniospinal irradiation (PCI) and total body irradiation (TBI). PCI or craniospinal irradiation is a major component of leukemia therapy, typically used for high risk patients and TBI is a standard component of bone marrow transplantation protocols [33, 34].

Tumors of the central nervous system (CNS), followed by leukemias and lymphomas are the most common RIMs seen and the risk of RIMs after radiotherapy persists longer and may be even life-long [35]. According to Neglia et al, meningiomas followed by gliomas are the most common CNS tumors in a case-control study of 14,361 childhood cancer survivors [9].

Radiation-induced meningiomas have following characteristic features, in contrast to sporadic meningiomas. a) Radiation-induced meningiomas are multiple [36]. b) They are aggressive in nature and commonly seen in younger age group [37].

Hematological malignancies like myeloid leukemias can be considered as RIM [38]. According to Boice et al, the risk of leukemia increases with increasing radiation doses up to 4 Gy, then decreases at higher doses [39].

### Effect of Radiotherapy Treatment Modality on RIM

Non-therapeutic scatter dose to tissues at a distance from the primary treatment volume has been postulated to be the reason of RIM arising in these areas because of low dose effects and are mainly carcinomas. While RIMs adjacent to the target volume, situated within high dose radiation portal, are generally of sarcomatous histology [40].

### Table 2. RIM After Radiotherapy for Breast Cancer

| Studies          | Site of radiation induced malignancy after radiotherapy for breast cancer | Comment                                                                                                                                                                                                 |
|------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Deutsch et al [21] | Lung (ipsilateral and contralateral)                                     | Higher dose of radiotherapy to lung in breast cancer patients of NSABP 04 in comparison to NSABP 06 trial was associated with increased incidence of subsequent RIM in both ipsilateral and contralateral lung. |
| Boice et al [22]  | Contralateral breast                                                     | The average radiation dose to the contralateral breast in this study was 2.82 Gy and less than 3% of radiation-induced breast cancer could be attributed to previous radiotherapy. |
| Zablotska et al [23] | Esophagus (squamous cell carcinoma (SCC))                              | Increases the risk of SCC not adenocarcinoma. As upper and middle third esophagus (commonest site of SCC) not the lower third (commonest site of adenocarcinoma) comes in the radiation portal. |
| Kirova et al [24]  | Sarcomas                                                                  | Thirty-five out of 16,705 patients of breast cancer developed sarcomas (13 sarcomas were located in the breast, five in the chest wall, three in the sternum, two in the supraclavicular area, one in the scapula, and three in the axilla). |

### Table 3. RIM After Pelvic or Genitourinary Irradiation

| Studies              | Primary malignancy | Increased risk of RIM                                                                                       |
|----------------------|--------------------|-------------------------------------------------------------------------------------------------------------|
| Chaturvedi et al [29]| Cervix             | Colon, anus/rectum, bladder, ovary, and genital sites                                                    |
| PORTEC-1 trial [30]  | Endometrium        | Gastro-intestinal malignancy                                                                             |
| Zelefsky et al [31]  | Prostate           | Skin, bladder and rectum                                                                                  |
| Van den Belt-Dusebout et al [32] | Testis | Stomach, pancreas, urinary bladder and kidney |
Intensity-modulated radiation therapy (IMRT) involves more fields for treatment; as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, IMRT requires longer beam-on time, which results in increase in the number of monitor units. Both factors are associated with increased integral dose, which tends to increase the risk of secondary malignancies. Therefore, according to Hall, IMRT may increase the incidence of RIM by 0.5% in comparison to the three-dimensional conformal radiation therapy (3D-CRT) [41]. IMRT likely doubles the incidence of RIM (from about 1% to 1.75%) in comparison to the conventional radiotherapy [3]. Combined scatter secondary radiation effects during IMRT delivery with neutron also contribute to out-of-field dose with a deposition pattern independent of the distance to the target treatment field [42].

A decrease in field size decreases normal tissue irradiation. According to Hodgson et al and Sasse et al, decrease in field size is associated with reduced incidence of RIM. By using involved field radiotherapy (IFRT) for HD, radiation-induced breast and lung cancers can be decreased [43, 44].

Fractionation in radiotherapy treatment is responsible for the majority of RIMs. However, a low rate of RIM has also been reported in case of stereotactic radiotherapy [45].

**RR of RIM After Radiotherapy**

Organs in the vicinity of the primary malignancy show different risk for development of RIM. The factors mentioned earlier (radiosensitivity of organ, planning technique and dosimetry) are mainly responsible for the difference in the RR. After going through the available literature, RRs of RIM in organs adjacent to primary breast, prostate and cervical malignancies, have been summarized (Table 4) [3, 46, 47].

### Conclusion

Radiotherapy is an important treatment modality in oncological care. RIMs are considered as one of the most significant and life-threatening late complications of radiotherapy. A number of general conclusions can be drawn from the above discussion.

1) Carcinomas and leukemias are commonly seen in organs receiving low dose radiation; whereas sarcomas are more common in tissues or organ receiving high dose radiation.

2) RIMs are more common with orthovoltage and high LET radiations.

3) Children are at higher risk as compared to adults, with chemotherapy and various hereditary disorders increasing the risk.

4) An increased incidence is observed with IMRT as compared to 3D-CRT due to the dose distribution (larger volume irradiated to lower doses).

Radiation therapy being one of the major treatment modalities of cancer can also sometimes cause cancer, hence truly can be considered a “two-edged sword”. RIM is a late and unavoidable side effect of radiotherapy, the exact pathogenesis of which is not well understood. Till date histology of RIM cannot be differentiated from natural occurring tumor.

### Conflicts of Interest

All authors declare that they have no conflicts of interest.
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