Review Article

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Radiation induced secondary malignancies: a review article

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Radiation-induced second malignancies (RISM) is one of the important late side effects of radiation therapy and has an impact on optimal treatment decision-making. Many factors contribute to the development of RISM such as age at radiation, dose and volume of irradiated area, type of irradiated organ and tissue, radiation technique and individual and family history of cancer. Exact mechanism of RISM is unknown. But nowadays, it is a growing concern in oncology because of the increased number of cancer survivors and efforts are being made to prevent or decrease the incidence of RISM. The primary search for articles was carried via Google Scholar and PubMed with keywords included 'radiation induced malignancies, second malignancies, and chemotherapy induced malignancies'. Additional papers were found through references from relevant articles. In this review article, we have discussed about the pathogenesis, factors contributing to RISM, screening and prevention strategies of RISM.

Keywords: Second malignancies, Radiotherapy, Chemotherapy

Introduction

Radiation therapy is an integral part of cancer treatment. More than 50% of all cancer-patients need radiation therapy at some point of the time. With advances in treatment modalities, number of long-term cancer survivors has significantly increased. Long-term cancer survivors are at increased risk of developing second malignancies. Studies have clearly shown that anti-cancer treatment has the potential to induce new primary (second) malignancies.

At present after surviving from a primary malignancy, 17%–19% patients develop second malignancy [1]. This is due to three reasons: continued lifestyle, genetic susceptibility, and treatment modality, i.e. radiotherapy (RT) and chemotherapy. RT contributes to only about 5% of the total treatment related second malignancies. However the incidence of only radiation on second malignancies is difficult to estimate because there are multiple factors that predispose the patients for second malignancies. In the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programme, it was observed that proportion of second malignancies was doubled in the last three decades (9% in 1975–1979 to 19% in 2005–2009 [1].

As children and young adults are likely to survive for a longer duration after anti-cancer therapy, they are at the greater risk of developing radiation-induced second malignancies (RISM). Follow-up data of the Childhood Cancer Survivor Study has shown that over the time, mortality has been increased due to second malignancies as compared to that due to other causes at 25 years after first cancer diagnosis [2,3].

In this review article we have summarized the current knowledge about treatment related secondary cancers. In particular, importance of radiation in development of second

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cancers is being highlighted. The primary search was carried via Google Scholar and PubMed with keywords included 'radiation induced malignancies, second malignancies, and chemotherapy induced malignancies'. Additional papers were found through references from relevant articles. This review article is discussed under four groups such as (1) pathogenesis (life style and environmental factors, genetic susceptibility, treatment, i.e., RT and chemotherapy), (2) contributing factors (age, gender, temporal association, RT technique, and RT type), (3) RT site (breast, prostate, gynecological malignancies, lymphoma, and pediatric malignancies), and (4) screening and prevention (screening for second malignant neoplasm [SMN] and intervention to reduce risk of SMN).

Pathogenesis

1. Lifestyle and environmental factors

The influence of smoking on the risk of treatment related lung cancer has been observed in several studies [4]. In Hodgkin lymphoma (HL) survivors, an international study has evaluated the risk of lung cancer in relation to radiation dose, chemotherapy and smoking [5]. The major risk (relative risk [RR] = 49.1) of lung cancer was seen among those who were moderate-to-heavy smokers and were treated with both RT and alkylating agents, with a RR of 7.2 as compared to non-smokers who were treated in the similar way. It was seen that after treatment of HL, 9.6% of all lung cancers were due to treatment, 24% of them were due to smoking and 63% of them were due to treatment and smoking in combination [6]. Several studies have observed that excess lung cancer risk following post-mastectomy RT is restricted to smokers, pointing to strong interaction [5].

Menopausal age has been shown to decrease the breast cancer risk in HL survivors and childhood cancer treated with chest RT [7]. In a Dutch study [8], 30% of female HL survivors reached menopause before age 41 (related to intensive chemotherapy). This early menopause was associated with around 60% (95% confidence interval [CI], 20%–80%) reduction in RT related breast cancer. Risk of breast cancer was 70% (95% CI, 40%–80%) less in those women having less than 10 years of intact ovarian function after RT as compared to those with 10–20 years of ovarian function after RT. Women having 20 years or more of intact ovarian function after RT may have 5.3 times (95% CI, 2.9–9.9) increased risk of breast cancer. Major risk reduction was observed in those who were treated before the age of 31. The risk reduction was not significant among those treated between 31 and 40 years of age, probably because this age is closer to natural menopause [8]. This indicates that ovarian hormones play a crucial role in promoting tumorigenesis once RT has produced an initiating event. A recent British study observed that patients who received RT close to menarche are more prone to develop breast cancer, suggesting greater carcinogenicity of radiation when the breast is developing [7].

2. Genetic susceptibility

Genetic susceptibility is a well-known fact for development of cancer. Many studies have investigated the risk of second malignancy in relation to specific genes that are involved in carcinogenesis and biologic pathways of drug metabolism. Recently, genome-wide association studies (GWAS) have identified rs4946728 and rs1040411 non-coding single nucleotide polymorphisms (SNPs) located on chromosome 6q21 as a risk factor for RISM in pediatric HL. Varszegi et al. [9] investigated the frequencies of the two SNPs (those identified in GWAS study) in healthy Hungarians and Romanians. The percentage of these SNPs was higher than those observed in controls and are in the range of the cases of the original GWAS study. It suggests that genetic characteristics of Hungarians are advantageous prior to the treatment of pediatric HL patients.

Acute myeloid leukemia and myelodysplastic syndrome are known complications of prior cytotoxic therapy [10]. Most cases occur 3 to 10 years after radiation or alkylating agents and accompanied by clonal unbalanced cytogenetic abnormalities, i.e., loss of chromosome 5 or 7 and mutation of *TP53* gene. Variants in drug metabolizing genes, DNA repair genes and genes that regulate hematopoietic environment are associated with increased susceptibility of treatment related leukemia [10]. This supports the thought of genetic susceptibility to treatment-related second malignancies.

3. Treatment

1) Radiotherapy

Carcinogenic potential of ionizing radiation is a well-known effect. Exposure to ionising radiation causes single strand and double strand DNA breaks (DSBs). Single strand breaks can be converted to DSBs during cell replication. DSBs can lead to gene mutation and subsequently malignant transformation of the irradiated cell [11]. Alteration in the DNA repair protein may also lead to increased risk of second malignancies. For example, ataxia telangiectasia mutated (ATM) is a protein that senses the DNA damage and initiates DNA repair cascade. Mutation in this gene can lead to increased radio sensitivity

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and cancer susceptibility [12].

Dose–response relationship for cancer risk prediction is usually obtained by analyzing retrospective cohort studies. At present, the largest amount of data is available from atomic bomb survivors in Japan. Studies on this cohort have found that most second cancers from RT occur in the volume irradiated by the primary radiation field, where the dose is in excess of 2.5 Gy. However, distant organs are also at risk, notably the lung, where the dose may be a fraction of a single Gy [13]. In addition to the type of tissue exposed and radiation dose, the time period over which the exposure occurs and the time after exposure are the key determinants of radiation induced cancer risk. For example, patients undergoing RT, who generally receive fractionated exposures of 1–5 Gy per fraction and cumulative doses of 15 to >50 Gy, have lower risks per unit dose than atomic bomb survivors, who received a single acute exposure primarily <2 Gy [14]. Finally, the time since exposure is an important determinant of subsequent cancer risk. Most radiation-related cancers are diagnosed only after decades of radiation exposure and the risk further increases by time [15,16].

2) Chemotherapy

Systemic anticancer treatment with chemotherapy and hormonal therapy are associated with increased risk of SMN. Treatment-related acute myeloid leukaemia (t-AML) and myelodysplastic syndrome (t-MDS) are the most established example [17]. Alkylating agents, topoisomerase-II inhibitors and antimetabolites have the highest leukemogenic potential [17]. Risk of t-AML and t-MDS is dose dependent after almost all alkylating agents and topoisomerase-II inhibitors. t-AML after alkylating agents has a latent period of 5–8 years and is mostly preceded by MDS [18]. However, latent period is <3 years after topoisomerase-II inhibitors and it is generally not preceded by MDS. Use of chemotherapy also increases the risk of solid malignancies, which typically occurs >10 years after exposure. Exposure to alkylating agents increase the risk of lung, thyroid, gastrointestinal and bladder cancer as well as sarcoma [19]. Association of bladder cancer with the exposure of cyclophosphamide is one of the examples that a specific alkylating agent has a carcinogenic potential for a specific site which is due to direct exposure of bladder epithelium to cyclophosphamide metabolites. Risk of gastrointestinal malignancies after procarbazine exposure is also an example of direct exposure.

Although chemotherapeutic agents have well established role in the development of SMN, rapid introduction of newer agents warrants further research with large sample size, longer follow-up with diverse patient population. This is important because combined modality therapy is being used for most of the cancer patients, so it becomes difficult to know the specific effect of a particular agent. Role of taxanes in t-AML is doubtful particularly due to frequent use of granulocyte colony stimulating factor (G-CSF) that also has leukemogenic potential [20]. Lenalidomide which is an immunomodulator also increases the risk of t-AML [21]. Role of monoclonal antibodies in development of SMNs is not very clear, however exposure to rituximab containing regimens increase the risk of AML [22]. Use of tamoxifen is associated with 2–5 times increase risk of endometrial cancer. However, effect of aromatase inhibitors on SMNs is not clear [23].

Contributing Factors

1. Age at radiation

Age at radiation exposure has a significant impact on development of RISM. Radiation exposure during childhood significantly increases the risk of second malignancy as compared to older population [24,25]. For a given dose, children are around 10 folds more sensitive to develop RISM as compared to adults [25].

2. Gender

Females have a greater propensity to develop RISM as compared to males [26,27]. This can be explained by the increased radiation exposure at a younger age due to high incidence of breast and thyroid cancers in female [28]. Several studies have indicated that for a given dose of radiation, women are more prone to develop second malignancy as compared to men [29]. Atomic bomb data is the best for showing females to be more susceptible to radiation induced cancers than in males [13,30]. This data has estimated that each Gray (Gy) of radiation increases the rate of solid cancers by about 35% (90% CI, 28%–43%) in males and 58% in females (90% CI, 43%–69%). Also for solid cancers as a group, women had absolute excess rate of second cancer than men (ratio of female to male, 1.4; 90% CI, 1.1–1.8).

3. Temporal association

In Japan atomic bomb survivors, initially patients were diagnosed with leukemia. Later on, after many years, solid tumors were diagnosed. Similarly in irradiated patients, latent period for the development of secondary leukemia is around 5–10 years while that for solid tumors is around 10–60 years

[13,30].

4. Radiation technique

Use of older radiation techniques have been shown to increase the risk of RISM [26]. Of late, there is a concern that increased use of intensity-modulated radiotherapy (IMRT) is associated with greater risk of RISM [24]. In IMRT technique, higher amount of normal tissue is exposed to low dose of radiation that may lead to higher integral dose and thus high risk of RISM. However, long-term follow-up data is required to draw a solid conclusion if IMRT really increases the risk of RISM. Another technical advancement in RT is image-guided radiation therapy (IGRT). Use of IGRT during set-up verification contributes to about 5%–20% of the total dose to normal tissues, situated outside primary treatment field [31]. Routine use of portal imaging or mega-voltage (MV) cone beam computed tomography (CT) may lead to exposures of up to 100 mGy per day that can increase the long-term risk of RISM [32].

5. Type of radiation

In a study by Chung et al. [33], the crude rate of second malignancies was lower in proton beam therapy (PBT) as compared to photons (5.2% vs. 7.5%). The probable reason for this is that the dose deposited by protons ends sharply nears the end of their range, giving rise to the Bragg peak while the dose deposition by photon is quasi exponential. This leads to higher integral dose in photons beam therapy (2–3 folds) as compared to protons. In a prospective study of 59 medulloblastoma patients who received PBT, no patient was diagnosed with second malignancy after a median follow-up of 7 years (range, 3.9 to 10.3 years) [34]. It was further compared to a case matched series of 43 patients who were treated with photons during the same period. It was observed that number of patients experiencing RISM was three in photon cohort while no patient developed RISM in proton cohort [35].

Sethi et al. [36] did a retrospective analysis to see the incidence of second malignancy among patients who received photon (31 patients) or proton beam radiation (55 patients) for retinoblastoma. Median follow-up was 6.9 years (range, 1.0 to 24.4 years) and 13.1 years (range, 1.4 to 23.9 years) for proton and photon cohort, respectively. It was observed that cumulative incidence of RISM or in-field second malignancies at 10 years was significantly high among the photon cohort (0 vs. 14%; p = 0.015).

Site of Radiation

In most cases it is difficult to assess the incidence of second cancers in the RT group because an appropriate control group is not available. The notable exceptions are prostate and cervical cancer where surgical options are available and provide a control group. In this paper, we have reviewed the previously published articles on radiation induced malignancies to look for excess risk of second malignancies in following site.

1. Breast

As the survival in cancer patients has been significantly improved during last few years, awareness about RISM is also increased [37]. Many studies have shown that irradiation for breast cancer increases the risk of second malignancies [38,39]. RISM mainly develops in the organs that are situated in the vicinity of irradiated area due to higher radiation exposure [38,39].

In a meta-analysis by Grantzau and Overgaard [40], RT for breast cancer significantly increased the risk of second non breast cancers with a RR of 1.22 (95% CI, 1.06–1.41). Even after 5 years of diagnosis, the risk remained significantly high with a RR of 1.12 (95% CI, 1.06–1.19). Lung and esophageal cancer are one of the common cancers after breast irradiation. Risk of lung cancer increased gradually with time followed by breast cancer radiation. After a latent period of 5, 10, and 15 years, RR of second lung cancer was 1.39 (95% CI, 1.28–1.51), 1.59 (95% CI, 1.39–1.81), and 1.66 (95% CI, 1.36–2.01), respectively. Risk of second esophageal cancer significantly increased after 5 or more years of breast irradiation. The RRs of second esophageal cancer at 5, 10, and 15 years of diagnosis was 1.53 (95% CI, 1.01–2.31), 1.56 (95% CI, 1.03–2.38) and 2.17 (95% CI, 1.11–4.25), respectively. There was also increased risk of radiation induced sarcoma by 2 folds with relative risk of 2.41 (95% CI, 1.41–4.13). However, previous RT did not increase the risk of second thyroid malignancies.

Hamilton et al. [41] analyzed 12,836 breast cancer patients who received either local (breast or chest wall) or locoregional (breast or chest wall and lymph nodes) radiation. The purpose of the study was to see if locoregional radiation increases the risk of second malignancies as compared to local RT alone. They found that the difference in the incidence of second malignancies was not statistically significant in both the groups.

2. Prostate

As already mentioned, prostate cancer is a good example of

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radiation-induced secondary cancers as surgery and RT both are equally efficacious for the treatment. Brenner et al. [42] have analyzed SEER database to compare second malignancy in prostate cancer patients who were treated with either surgery or RT. They inferred that RT for prostate cancer significantly increased the risk of second malignancies by approximately 6% (95% CI, 1%–11%) as compared to surgery (p = 0.02). Increased relative risk was 15% and 34% for those who survived ≥5 years and ≥10 years, respectively. Majority of the second cancers were bladder and rectal cancers. However, incidence of secondary lung cancer and sarcomas in radiation field also increased (lung received, 0.5 Gy). In a study to assess the impact of radiation among prostate cancer patients, overall rate of second solid cancer was similar in both 3D-CRT and conventional RT arm (RR = 1.00; 95% CI, 0.91-1.09) [43]. However, the risk of a second rectal cancer was significantly lower in the 3D-CRT arm as compared to conventional RT (RR = 0.59; 95% CI, 0.40–0.88). Rates of second cancer diagnosis (site specific solid cancer and leukemia) were equal for both higher and lower-energy RT (RR = 0.97; 95% CI, 0.89–1.06). When brachytherapy was compared to external beam RT (EBRT) patients, there were lower rates of second solid cancers overall (RR = 0.92; 95% CI, 0.83–1.02), significantly lower rates of second colon cancer (RR = 0.52; 95% CI, 0.37–0.73), and leukemia (RR = 0.60; 95% CI, 0.40–0.89).

3. Gynecological malignancies

Chaturvedi et al. [44] analyzed a data of 104,760 cervical cancer patients who were reported to various population based cancer registries. In this cohort 52,613 patients received RT. Patients who were treated with RT were at increased risk of second cancer (colon, rectum, anal canal, ovaries, uterus and other pelvic structures) even after 40 years of follow-up as compared to general population. After modification with age, patients who were diagnosed with cervical cancer at early age were at increased risk of second cancer.

In PORTEC-1 trial endometrial cancer patients were randomized to receive either RT or observation. It was found that at a median follow-up of 15 years, 22% and 16% patients developed second malignancies in RT versus observation group, respectively. Incidence of gastrointestinal malignancy was almost doubled in RT group (6.2%) as compared to observation group. Gastrointestinal malignancy was also the commonest second primary in RT group [45].

4. Lymphoma

The risk of second malignancy is a major concern in HL patients due to young age at diagnosis and excellent survival. HL survivors are at increased risk of second malignancy as compared to general population and these are breast, lung, colorectal, thyroid, sarcoma and stomach cancer [46]. Likewise, RT for non-Hodgkin lymphoma (NHL) also increases the risk of both solid malignancies and leukemia [47]. Younger age at radiation, increased dose of radiation, larger radiation field, i.e., mantle field, administration of cytotoxic agents are risk factors for second malignancies [48].

5. Pediatric malignancy

There has been increased risk of second malignancies after chemoradiotherapy for pediatric cancer patients as compared to general population [26]. Incidence of second cancer and late adverse effects after childhood cancer treatment has been explained by the Childhood Cancer Survivor Study. In a study of 20,346 childhood cancer survivors who were diagnosed from 1970 to 1986, it was observed that cumulative incidence of all second malignancies was 20.5% after 30 years of diagnosis. The risk of second malignancies was higher in those who had received RT [26]. Similarly, in a cohort of British childhood cancer survivors (British Childhood Cancer Survivor Study), the absolute excess risk of all types of second malignancy was 19% (95% CI, 11.7%–26.3%) after a median follow-up of 24.3 years. Overall, the risk of SMNs was four times higher than expected. Absolute excess risk was 16.8 per 1,000 person years (95% CI, 15.3–18.3). They concluded that risk of SMN was significantly associated with type of childhood cancer, RT, chemotherapy and current age (p<0.001) [49]. In a retrospective study by Henderson et al. [50] it was seen that the incidence of gastrointestinal second malignancies was 4.6 times higher in childhood survivors as compared to general population. Higher risk was associated with abdominal irradiation, high dose procarbazine and use of platinum drugs. Effect of prophylactic cranial irradiation (PCI) was observed in a study from St. Jude Children's Research Hospital. In this study, 1,600 patients of acute lymphoblastic leukemia received PCI after chemotherapy. Increased incidence of secondary glioma and meningioma was observed in these patients during 20 years of follow-up. Incidence of brain tumors was higher if age at RT was younger than 6 years and among those, who received high radiation dose [51].

Literature review on RISM is tabulated, showing age at the time of primary tumor, radiation dose, incidence of second neoplasm, and time gap between primary treatment and second malignancy (Table 1).

Table 1. Literature review on RISM (original)

S. No	Study/year	Primary tumor	No. of patients	Age at primary tumor (yr)	Treatment received (% of patients)	Radiation dose (Gy)	Incidence of second primary	Second neoplasm	Time gap between primary treatment and second primary (yr)
1	Friedman et al. [26] 2010	Childhood[a)]	14,359	5–56 (median 30)	Surgery alone (6.3) Radiotherapy alone (10.5) Chemotherapy and radiotherapy (49) Chemotherapy alone (21.5) None (13)	2.2–52.6	20.5 (cumulative at 30 years)	SMN (7.9%) Non-melanoma skin cancer (9.1%) Meningioma (3.1%)	5–32.5 (median 17.8)
2	Brenner et al. [42] 2000	Prostate	51,584	70.3 (mean)	Radiotherapy alone Surgery alone Radiotherapy and Surgery		3,549 cases	Second neoplasm[b)]	5– >10 (range)
3	Inskip et al. [62] 2009	Childhood[a)]	6,647	<21	Radiotherapy alone Chemotherapy and radiotherapy	0.13–60	148 (2.3%)	Breast	5–32 (range)
4	Bhatti et al. [63] 2010	Childhood[a)]	12,547	<21	Radiotherapy alone Chemotherapy alone Chemotherapy and radiotherapy	0– >40	119 cases	Thyroid	5– >25 (range)
5	Travis et al. [64] 2003	Hodgkin's disease	3,817	<30	Radiotherapy alone Chemotherapy alone Chemotherapy and radiotherapy	37.7 (median)	105 cases	Breast	1– >25 (range)
6	Rubino et al. [65] 2005	Breast	6,597	20–91 (median 55) <50 years (40%)	Radiotherapy (73.3) No radiotherapy (26.6) Chemotherapy	57.9 (median)	14 cases	Soft tissue sarcoma and bone sarcoma	1–37 (median 7.9)
7	Bioce et al. [66] 1988	Cervix	150,000	52 (mean)	Radiotherapy (97.6) Brachytherapy only (16.8) External beam radiotherapy only (3.2) External beam and brachytherapy (72.5%)		4,188 cases	Second neoplasm[c)]	1– >30
8	Gilbert et al. [67] 2003	Hodgkin's disease	19,046	37– >56	Radiotherapy alone Chemotherapy alone Chemotherapy and radiotherapy	32 (median)	227 cases	Lung	1– >20
9	Taylor et al. [68] 2010	Childhood[a)]	17,980	<15	Radiotherapy (51.2) No radiotherapy (21.3) Chemotherapy (36.8) No chemotherapy (33.5)	0.01–>40	247 cases	Meningioma (137) Gliomas (73) Other CNS tumors (37)	20.5 (mean)
10	Morton et al. [69] 2012	Breast	289,748	28–88	Radiotherapy alone Chemotherapy alone Chemotherapy and radiotherapy No chemotherapy and radiotherapy	40–50	252 cases	Esophagus	5–37 (range)

RISM, radiation-induced second malignancies; SMN, second malignant neoplasm; CNS, central nerve system.

[a)]includes leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, bone cancer, central nervous system malignancy, or kidney cancer.

[b)]includes bladder, rectum, colon, lung, sarcomas in field, distant sarcomas, and leukemia.

[c)]includes breast cancer was most common second cancer, stomach, colon, rectum, ovary, uterus, leukemia, all lymphomas, pancreas, bladder, kidney, and other genital organs.

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Screening and Prevention

1. Screening for SMN

Research on the screening of cancer survivors has largely focused on breast cancer after HL and childhood cancer. National recommendations on screening have been produced in the UK [52] and USA [53], recommending that screening should be started at a younger age (age 25–30 years, or 8 years after treatment) with more frequent intervals (annually) and should involve more modalities (MRI, ultrasound, mammography, alone or in combination) than in general population program. Studies have shown that 80%–100% of tumors are detectable by mammography and recall rate is greater than that after general population screening [54]. Breast cancers diagnosed after HL have been found more likely to be screen-detected and more likely to be diagnosed at an earlier stage, than those in the general population. There is some indication that the introduction of screening may have led to earlier stage diagnosis. For many cancers with increased risks among certain cancer survivors such as lung and stomach, no known screening method can affect prognosis.

2. Intervention to reduce risk of SMN

Developing intervention strategies to reduce the incidence of SMNs is an attractive goal. For HL patients, RT is identified as one of the main cause of second malignancies. [15] Therefore, the wide field 'mantle' [55] and 'inverted Y' [55] techniques, the mainstay of HL treatment in the 1960s and 1970s, were gradually replaced by much smaller involved field approaches [56]. More recently 'involved node' [57] and 'involved site' [58] fields have been developed. 'No radiotherapy' strategies have also been investigated. More recently, response-adapted approaches whereby treatment is adjusted according to initial response have been investigated in HL.

Interventions to reduce the risk of SMN can be considered during or following treatment for the first cancer. In young women who have received radiation of breast tissue at younger age and are at high risk of breast cancer, anti-estrogens such as tamoxifen or interventions to temporarily delay onset of menarche may be protective. As the risk of breast cancer after chest RT at young ages is comparable to that of *BRCA* mutation carriers [59], bilateral prophylactic mastectomy may also be an appropriate consideration in some patients, especially when they also have a family history of breast cancer [60]. Lifestyle interventions after treatment such as quitting smoking, reduce alcohol consumption, regular exercise and weight loss may be effective in reducing the incidence of SMNs and should be evaluated in appropriately designed clinical trials [61].

Conclusion

Radiotherapy has been considered as a double edged sword as it has a well-established role in the management of solid cancers but unfortunately it is likely to induce cancers years after the treatment. Risk of RISM is a main concern especially in pediatric population due to increase number of survivors. One of the main reasons is that patients who receive RT are at high risk of developing second cancer because of their lifestyle and genetic predisposition. This factor can be even more important than risk of radiation. But as of now, only little information is available about those factors which can modify the risk of second malignancies like genetic variants, lifestyle or environmental factors.

In many countries, recommendations on screening for second malignancies (especially breast cancer) have been developed for selected high-risk survivor groups. However, most guidelines are consensus-based rather than evidence-based. Effective screening is only possible with better understanding of the pathogenesis of treatment-related secondary cancers. Currently such knowledge is lacking, so there is a strong need for studies investigating the mechanisms by which different treatments affect the pathogenesis of second malignancies, the clinicopathological characteristics of treatment-related cancers and their prognosis. Integrated research involving clinical studies, radiobiology and physics are important to estimate and to reduce the risk of treatment related second cancers.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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