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Radiation-induced tumors and secondary malignancies following radiotherapy

Tumori indukovani zračenjem i sekundarni maligniteti posle radioterapije

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Introduction

Radiotherapy (RT) is an integral part of multidisciplinary cancer management and is indicated by evidence-based guidelines in more than 50% of all cancer patients [1]. State-of-the-art RT techniques such as intensity-modulated radiotherapy (IMRT), image-guided RT, and proton therapy have decreased the risk of cancer recurrences, improved target dose coverage with dose escalation, reduced treatment toxicities, and improved survival.

Potentially adverse effects of these treatments can reduce the quality of life and lead to morbidity and even mortality in cancer survivors. Regarding RT treatment, toxic effects are generally divided into early and late effects. Early toxic effects of radiation on healthy tissue are reversible and develop due to acute inflammation, whereas late adverse effects mostly remain permanent and are caused by chronic inflammation, microvascular damage, fibrosis, and radiation-induced genetic instability [2].

Long-term cancer survivors treated with RT treatment are at greater risk of developing late effects, including the development of radiation-induced malignancy (RIM) [2]. In 1948, Cahan et al. [3] defined a radiation-induced sarcoma, while nowadays, in practice, modified Cahan's criteria for the definition of RIM are used [4]. These criteria include that RIM must arise within the treatment field, with a significant latent period, and have different histology than primary malignancy (moreover, the origin of tissue of RIM must be metabolically and genetically normal before irradiation).

Cancer patients are at higher risk of developing a second malignancy (SM) compared to the general population. However, subsequent neoplasms may not be associated with prior cancer treatment, and RIMs make only a small proportion of SMs [5].

The risk of developing RIM after RT treatment varies on multiple factors, such as patients' age at the time of radiation, genetic susceptibility, patients' family history of cancer, lifestyle and environmental factors, the organ and tissue site receiving radiation, RT treatment modality, and dosimetric characteristics of the RT plan [2, 6].

Children are considered 10 times more sensitive to the carcinogenic effect of radiation than adults. Several studies found that pediatric cancer patients who underwent RT have a greater risk of developing RIM than adults [7, 8]. These malignancies may lead to a decrease in the overall survival after the treatment of primary cancer [2, 9].

When assessing the risk of developing RIM regarding gender, studies have shown that females are at greater risk compared to males [10]. Unfortunately, the irradiation of the breast tissue during RT treatment in Hodgkin's lymphoma is well known as a risk factor in inducing breast cancer. Previously published studies have reported that menopausal and ovarian function status in correlation with age in female patients affects the risk of developing RIM in cancer survivors treated with chest RT for Hodgkin's lymphoma. Namely, early menopause, as well as ovarian dysfunction at a younger age, may reduce the risk of breast cancer as a RIM [11].

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The dose-response relationship for radiation carcinogenesis as well as long-term effects of radiation on the development of RIM in humans are explored in Japanese atomic bomb survivors, in whom leukemia was initially diagnosed with a latent period of 5–10 years, and afterward, solid tumors with a latent period of 10–60 years (Figure 1). The latent period for developing RIM in irradiated patients is reported to be similar to that in Japanese atomic bomb survivors, and the risk continues to increase with decades gained after the exposure [7, 12].

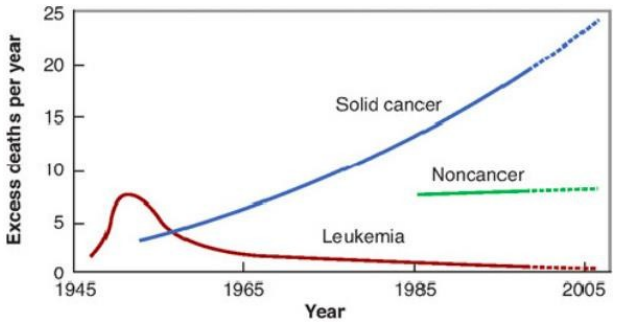

Fig. 1 – Time course of second malignant neoplasm development following A-bomb explosion in 1945. Leukemia appeared first, followed by solid cancers several years later. There was also an excess of noncancer deaths from stroke and heart disease by the late 1980s [9].

RT patients receive a high dose of radiation at a low volume and significantly lower doses at larger volumes. However, RIMs can arise from the high-dose irradiated tissues, as well as from the low-dose irradiated tissues, e.g., organs that are distant from the radiation field [13].

Cancer patients are often treated with combined treatment modalities, so it may be difficult to define the specific effect of a particular agent. Exposure to chemotherapeutic agents may be associated with an increased risk of SM neoplasms, such as anthracyclines and alkylating agents with sarcoma [14], alkylating agents with carcinomas [15], and cisplatin-based therapy with solid tumors after testicular nonseminomas [16]. Treatment-related myeloid neoplasms, including therapy-related acute myeloid leukemia and therapy-related myelodysplastic syndrome, may be linked with exposure to alkylating agents, as well as topoisomerase (TOP) II inhibitors [17].

The most frequent malignancies associated with RIMs

For the adult population, clinical data on RIM development are best reported for breast and prostate cancer due to the high rate of long-term survival. To assess the incidence of developing RIMs, an appropriate control group should be available, which is often difficult to provide; notable exceptions are prostate and cervical cancer, where patients treated with surgery provide control groups.

RT is an essential adjuvant part of breast cancer treatment, which reduces disease recurrence and improves overall survival. However, RT can also be associated with an increased risk of second cancer in exposed sites.

Radiation-induced sarcoma is a rare complication of breast irradiation with an increased risk of appearance over time after RT [18, 19]. According to Salminen et al. [18], the most common site of radiation-induced sarcoma was breast soft tissue (Figure 2), while the prevalent histological subtype was angiosarcoma.

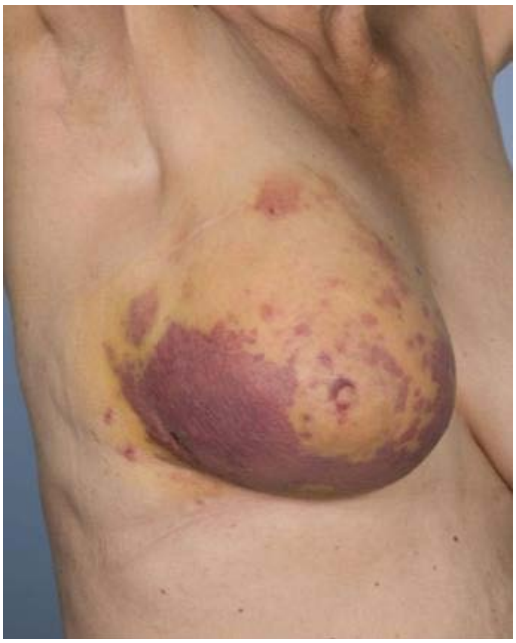

Fig. 2 – The typical appearances of radiation-induced angiosarcoma of the breast [19].

According to the large meta-analyses conducted by Grantzau and Overgaard [20], RT treatment of breast cancer has significantly increased the risk of non-breast SMs with a relative risk (RR) of 1.22. The risk remained elevated, even 5 years after diagnosis, with a RR of 1.12. The most common SM sites were lung and esophageal cancers and soft tissue sarcoma. The estimated RRs for these sites were 1.23, 1.17, and 2.41, respectively. After a latency time of at least five years from breast cancer diagnosis, the incidence of SM gradually increased. A significant association between RT of breast cancer and second thyroid cancer was not found.

Berrington de Gonzalez et al. [21] estimated the long-term cancer risk of all solid cancers in a large cohort of patients after breast cancer RT. In the study, SM sites were divided into three dose groups (high: 1+ Gy; medium: 0.5–0.99 Gy; and low: 0.5 Gy; dose sites) according to the mean organ dose from the RT treatment. Estimated RRs were increased for the group of sites that received the highest radiation exposure (1+ Gy: lung, esophagus, pleura, bone, and soft tissue; ~1 Gy: contralateral breast cancer), while for lower dose sites, RRs were not elevated. They even found that most of the solid SMs were also related to other risk factors such as lifestyle and genetic factors.

Regarding secondary sarcomas, both studies also showed that RRs were especially highly elevated for angiosarcomas.

In the study by Mladenovic et al. [22], tumor responses and long-term outcomes were analyzed in 134 patients with

non-inflammatory locally advanced breast cancer treated with preoperative RT. Their results of pathological complete tumor response to preoperative RT were in agreement with similar previously conducted trials. The occurrence of SM was detected as breast cancer in the contralateral breast in two patients and papillary thyroid cancer in one patient.

RIMs are reported in long-term survivors of prostate cancer. Fontenot et al. [23] estimated that proton therapy reduced the risk of RIM by 26% compared to 39% with contemporary IMRT in prostate cancer patients. When comparing the risk of developing a SM treated with RT vs. surgery, Brenner et al. [24] published that RT significantly increased the risk of SMs by about 6% (p = 0.02). For patients who survived for ≥ 5 and ≥ 10 years, the increased RR was 15% and 34%, respectively. The vast majority of second solid cancer sites were bladder, rectum, and lung cancers, as well as sarcomas within the treatment field, while no significant increase in rates of leukemia was noted.

Chaturvedi et al. [25] reported that irradiated cervical cancer patients were at increased risk of SMs even after 40 years of follow-up compared to the general population. The risk of SMs was increased at sites close to the cervix, including anal, colorectal, and genitourinary sites.

Rodriguez et al. [26] analyzed the risk of developing colorectal cancer among long-term survivors of cervical cancer who received RT. Results of the study implied that RIM of the colon and rectum might occur 8 years after RT for cervical cancer. Furthermore, these patients treated with radiation at a young age should start screening for colorectal cancer earlier than the age recommended for low-risk individuals (approximately 8 years after the treatment).

Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial, in which patients were randomly assigned into irradiated (postoperative external beam RT) and observational groups, has shown that after 15 years of follow-up, 22% of patients were diagnosed with second primary cancer in the RT group vs. 16% in the observational group. The most common cancer type in irradiated patients was gastrointestinal cancer [27].

Many studies have published an increased incidence of SMs in patients treated with RT for Hodgkin's and non-Hodgkin lymphoma. Factors contributing to the higher incidence of RIMs in Hodgkin's lymphoma are the following: relatively young patients, high curability, large irradiation field, the technique used in past decades, and combined therapeutic modalities, including cytotoxic drugs. The majority of SMs were thyroid, breast, lung, and stomach cancer, as well as sarcoma [28]. Moreover, RT increases the risk of developing both solid tumors and leukemia for non-Hodgkin lymphoma survivors [29].

With an increasing number of long-term cancer survivors of childhood malignancy, the occurrence of the second SMs has risen. Primary cancer treatments, including RT and chemotherapy, are associated with the risk of second malignant neoplasm (SMN) after primary childhood cancer.

The Childhood Cancer Survivor Study (CCSS) analyzed the incidence and risk factors of subsequent neoplasms after treating childhood cancer. It was reported that the cumulative incidence of all subsequent neoplasms was 20.5% thirty years after diagnosis, whereas radiation exposure was associated with an increased risk of SMs. Regarding subsequent neoplasm subtype, the 30-year cumulative incidences were 7.9%, 9.1%, and 3.1% for SMNs (excluding non-melanoma skin cancer), non-melanoma skin cancer, and meningiomas, respectively (Figure 3). The most commonly diagnosed SMs were bone, thyroid, head and neck cancer, breast cancer, central nervous system malignancies, and soft tissue sarcoma [30].

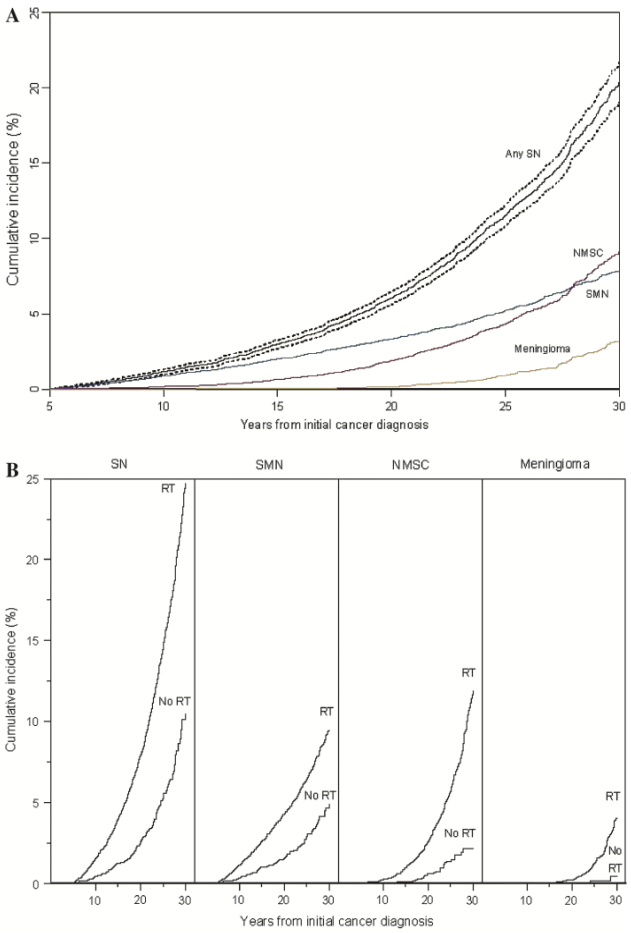

Fig. 3 – Cumulative incidence of second neoplasms (SNs) at 30 years after an initial cancer diagnosis: A) All SNs [cumulative incidence of any SN, non-melanoma skin cancer (NMSC), second malignant neoplasm (SMN), and meningioma are shown]; B) All SNs stratified by radiation therapy (RT) treatment or no RT [30].

Research of SM etiology in childhood cancer survivors is extremely important as their good prognosis enables a long period for SM occurrence. Although pediatric patients have fewer exposures to lifestyle and environmental cancer risk factors, trials of childhood cancer survivors can provide additional insight into the role of primary cancer treatments in SM etiology [31].

Genetics of radiation-induced tumors and toxicities

Radiation sensitivity is not a monogenetic trait but rather a polygenetic trait where the majority of the population

is located in the middle of the normal distribution of expression. People with mutations that could be associated with higher sensitivity to radiation, such as mutations concerning DNA repair mechanisms, might have a higher risk of developing early or late toxicities, and a possibility for deceleration of the treatment dose can be considered [32].

Nowadays, the carcinogenic effect of radiation is well-documented. Genetic susceptibility plays an important role in the pathogenesis of RIMs. Radiation can cause DNA damage to normal cells, which might lead to genomic instability and, finally, but rarely to RIM. A recent study from the University of Utah School of Medicine, published in 2017, showed that 13% of patients who received RT for breast cancer developed a SM with a median follow-up of 8.9 years, and it was estimated that only 3.4% of SMs were attributable to radiation therapy [33].

Although radiation sensitivity is largely explained as a polygenic trait encoded by numerous common variants with small individual effects, there are pathogenic mutations that cause rare conditions and have a monogenetic pattern of inheritance. Patients with these genetic syndromes are prone to developing malignancy (higher baseline risk of cancer development), and some of them have an increased risk of RIM. Some of these conditions are ataxia telangiectasia [autosomal recessive mutations of ataxia telangiectasia mutated (ATM) serine/threonine kinase gene], familiar cancers of the breast and ovarium due to breast cancer susceptibility genes (BRCA) mutations, hereditary retinoblastoma, and Li Fraumeni syndrome (both are autosomal dominant and caused by a mutation in RB1 or TP 53 gene, respectively), as well as Gorlin syndrome, neurofibromatosis type 1 and Nijmegen breakage syndrome [32, 34].

The most commonly studied heterozygous mutations are ATM and BRCA heterozygotes [34–36]. It is well known that the homology-directed repair route mediated by products of BRCA genes is activated in only 15% of DNA double-strand brakes caused by therapeutic radiation, so it should be no surprise that the clinical data consistently demonstrate no increased risk in BRCA heterozygous patients treated with standard adjuvant radiation regimens [36]. On the other hand, ATM serine/threonine kinase is directly involved in double-strand break repairs, but the clinical data on its importance in developing radiation sensitivity is contradicted. It seems that there is no increased risk of developing radiation toxicities in heterozygote carriers of pathogenic ATM mutations, but in the SEER clinical trial in breast cancer patients, an increased risk of developing contralateral breast carcinoma was observed in the irradiated group (probably due to scattering radiation) [35, 37]. Pathological ATM mutations are still not a contraindication for RT treatment. Notably, individuals with genetic syndromes with an increased risk of developing several types of cancer should be monitored for SMNs after RT treatment.

To develop a personalized medical approach in RT, with better tumor response, lower radiation toxicity, and without dose escalation, many trials explore the molecular signature concept of radiosensitivity. It would be beneficial to identify predictive biomarkers of the initial response to RT that could be helpful for predicting clinical outcomes in patients treated with RT. Tanić et al. [38] published that the MAP3K4 gene could be a potential biomarker response to RT and a potential target for radiosensitizing combination therapy.

In a genome-wide association study, Best et al. [39] identified two variants (rs4946728 and rs1040411 noncoding single nucleotide polymorphisms, located between PRDM1 and ATG1 genes) on chromosome 6q21 associated with the risk of SMNs after RT in pediatric Hodgkin's lymphoma survivors. This data indicates the significance of genetic susceptibility to SM etiology.

Testing for somatic mutations (mutations present in the tumor itself) is the most frequent scenario when cancer patients come in contact with genetic testing. Mutations in tumors occur at a higher rate than in normal tissues due to genetic instability, and their genetic information is different from the genetic information of the patient. These mutations have implications mainly for tumor response and tumor treatment decisions [32].

The somatic mutation pattern (genetic signature) could also be of diagnostic importance. Several studies have shown that RT could have its' molecular signature on the treated area, which can be detected in SMs that develop later. For instance, upregulation of MYC, RET, and FLT4 with down-regulation of CDKN2C and PRDM1 genes are frequent in radiation-induced sarcomas and other radiation-induced malignancies [40, 41].

On the other hand, somatic mutations of the key genes involved in DNA repair mentioned above can change the radiobiological behavior of the tumor. Usually, pathogenic mutations involved in DNA repairs such as ATM or BRCA 1 and 2 could be expressed at a higher rate and/or be of higher penetrance in the tumor, more than in the normal tissue due to loss of heterozygosity. In such a scenario, a full expression of recessive mutations and/or full penetrance of dominant mutations such as ATM and BRCA, respectively, can make the tumor more radiosensitive [42]. On the other hand, somatic mutations in k-RAS can make a tumor more radioresistant [43].

The effects of radiation modalities on RIM development

Nowadays, different types of ionizing radiation are used for cancer treatment that can be divided roughly into two groups: photon and particle radiation. High energy photons damage cellular molecules by producing highly reactive O_2 species, which react further with cell molecules, especially DNA. Radiation can cause single or double breaks of the DNA helix, which results in the loss of proliferation ability and cell death [44]. The biological effectiveness of ionizing radiation is quite dependent on the so-called linear energy transfer (LET), which represents the energy deposited in the targeted tissue [45]. Compared with particle radiation, photons have lower LET.

Proton beams have the highest transfer in one particular point in the body, followed by a sharp decrease of LET with the effect of sparing surrounding tissue. This point can be

manipulated, so better dose distribution and maximum dose deposition in the volume at the targeted area can be achieved while sparing the other structures along the beam way. This property gives proton therapy an advantage in treating tumors, where sparing the normal tissue is an imperative [46]. However, high LET radiation is more likely to produce cell death and mutation than low LET radiation [47, 48].

Studies that compare the incidence of SM in long-term cancer survivors following proton and photon beam therapy are limited. However, available data suggest a lower incidence of RIM in patients treated with proton beam therapy compared to photon therapy [49]. Chung et al. [50] published a comparative analysis of incidence rates of SM after radiation for cohorts of proton and photon-treated patients. After a median follow-up of 6.7 and 6.0 years in proton and photon-treated groups, the rate of SM was lower among patients treated with proton radiation compared to patients treated with photon RT (5.2% vs. 7.5%, respectively).

With the advances in RT, from conventional and three-dimensional conformal RT (3D-CRT) to IMRT and volumetric-modulated arc therapy, radiation is delivered to the targeted areas more precisely with dose escalation, and the organs at risk are better spared. As a complex radiation technique, IMRT, compared to 3D-CRT, is associated with better organ risk management and decreased frequency of acute and chronic treatment toxicities, followed by improved quality of life after treatment [51, 52]. The study by Hall and Wuu [53] showed that the move from 3D-CRT to IMRT can lead to an increase in RIMs. The rationale for this theory is that IMRT requires many fields, irradiating a larger volume of healthy tissue (so-called "low-dose bath"). Moreover, IMRT requires twofold to a threefold larger number of monitor units to deliver a preset dose compared with 3D-CRT. This larger number of monitor units leads to X-ray leakage and distant tissue irradiation. Considering that IMRT and volumetric-modulated arc therapy are fairly modern techniques and that the development of RIMs takes years and even decades, few studies compare risk in RIM development between novel techniques and 3D-CRT. However, we can assess that risk using different models. For instance, the concept of organ equivalent dose can be used to calculate the risk of RIM development in different tissues when three-dimensional dose distribution RT techniques are used [54].

Image-guided brachytherapy based on MRI, with radioactive source Ir-192, has become a standard treatment in gynecological malignancies. It provides precise information about radiation dose distribution, target volume coverage, and doses delivered to organs at risk while decreasing the toxicity [55].

Conclusion

As the number of long-term cancer survivors after RT increases, the RIMs are becoming a relevant clinical problem in long-term follow-up. RIMs are important late adverse effects of RT that can directly impact patient management and treatment decision-making. These facts could modify initial work-up, treatment, and follow-up protocols. Inclusion of genetic testing, further investigation of novel RT techniques, and additional screening and surveillance strategies should be added to the overall cancer care.

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