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Radiation-induced breast cancer in women with Hodgkin's disease

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ABSTRACT

Aim and background: The aim of this study is to analyze the main clinical and pathologic characteristics of radiation-induced breast carcinomas (BC) following treatment for Hodgkin's disease (HD) and to identify the risk factors for their induction. To create a mathematical model for the prediction of expected age at which a BC might develop based on the age at treatment for HD.

Materials and methods: Thirty-nine cases of women with BC that developed after treatment for HD in puberty or adolescence were analyzed retrospectively. The median age at initiation of treatment for HD was 12.9 years (9–21). The median age at diagnosis of the second malignancy – breast carcinoma was 32.4 years (22.9–39).

Results: The distribution of patients according to the clinical T stage of breast cancer was as follows: 11 patients with T1 stage BC (28%), 22 with T2 stage (56%) and 6 with stage T3 (16%). Prevalent were tumors localized in the lateral breast quadrants. The observed 5 year survival was 95%.

Conclusion: The risk of solid tumors, especially breast cancer, is high among women with HD disease who were treated with radiotherapy in their childhood. In this article, we propose a specific mathematical age formula which could be used as predictive equation when the age of the treatment for HD is in the range between 9 and 21 years. Systematic screening for breast cancer in these patients would be significantly important for their health and could improve their survival.

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1. Background and Aim

One of the major medical successes in modern day protocols for treatment of hematologic diseases are the results achieved in the complex therapy of Hodgkin's disease (HD).[1] With the continued overall survival of these patients, an increase in the frequency of radiation-induced tumors is observed. A series of investigations have demonstrated an elevated risk for second malignancies in patients treated for Hodgkin's disease.[2–4] Acute nonlymphocytic leukemias, non-Hodgkin's lymphomas, breast and gastrointestinal carcinomas have been described.[5–7] Breast cancer is the most common solid tumor that develops in women following combined curative treatment with chemo- and radiotherapy for HD.

Previously published data indicate that radiation-induced breast cancer presents a serious medical problem. In the study of Bhatia et al. on the late effects of treatment of HD, 88 secondary neoplasms were detected in 1380 patients with HD. Breast cancer was the most common solid tumor (standardized incidence ratio 75.3; 95 percent confidence interval, 44.9–118.4), with an estimated actuarial incidence in women that approached 35 percent (95 percent confidence interval, 17.4–52.6 percent) by 40 years of age.[8] To solve this problem, scientific research in recent years has focused on the following areas:

- Identification of risk factors for the development of radiation-induced breast cancer;
- Investigation of their clinical and pathological characteristics;
- Proposals for methods for the monitoring of patients treated for HD and the introduction of new therapeutic approaches;

2. Materials and methods

We present the results of our own clinical material consisting of 39 cases followed up retrospectively. Patients have been treated for HD during childhood and puberty and have developed breast cancer after a period of 11–23, median period – 17 years.

Tumor localization, tumor stage and the histology of the tumors are represented in Table 1, while Table 2 shows the distribution of patients according to their N stage, grade of malignancy (G), the presence of lympho-vascular invasion (LVI), hormonal and HER 2 receptor status.

Frequency distributions; χ^2-square test were used for the statistical processing of the data; Kaplan–Meier – for survival analysis, graphical methods, etc.

Upon examination of the linear correlation between the age at treatment for HD and the age at diagnosis of breast cancer a coefficient of linear correlation between the two variables – $r = 0.614$ was established. Correlation degree of dependence was classified as follows: (1) extremely high – $r \geq 0.9$; (2) great $0.9 \leq r \leq -0.7$; (3) substantial $r \leq -0.5 \leq 0.7$; (4) moderate $r \leq -0.3 \leq 0.5$; (5) weak – $r \leq 0.3$.

Table 1 – Tumor localization, tumor stage and tumor histology.

Localization of the tumor in the breast	No. of patients (%)
Lower – medial quadrant	7 (18%)
Lower – lateral quadrant	10 (26%)
Upper – lateral quadrant	7 (18%)
Centrally located	12 (31%)
Upper – medial quadrant	3 (7%)
T stage	
pT1a	0 (0%)
pT1B	2 (5%)
pT1c	9 (23%)
pT2	22 (56%)
pT3	6 (16%)
Histological type	
ductal in situ	5 (14%)
lobular in situ	0 (0%)
invasive ductal	17 (44%)
Invasive lobular	16 (41%)
Papillary	1 (3%)

T – tumor stage.

Table 2 – N stage, G, LVI, hormonal status, HER 2 status.

N stage	No. of patients (%)
pN0	12 (32%)
pN1a	13 (33%)
pN2a	7 (18%)
pN2b	4 (10%)
pN3b	3 (7%)
G	
G1	6 (15%)
G2	13 (33%)
G3	20 (51%)
LVI	
LVI (–)	22 (56%)
LVI (+)	17 (2%)
Hormonal status	
ER, PR (+)	22 (56%)
ER, PR (–)	17 (44%)
HER 2 status	
HER 2 (3+)	14 (36%)
HER 2 (–)	25 (64%)

N – lymph nodes, G – degree of malignancy, LVI – lymph-vascular invasion, hormonal ER, PR – estrogen and progesterone receptor status, HER 2 status.

3. Results

The distribution of the patients according to the clinical T stage of breast cancer was as follows: 11 patients with T1 stage BC (28%), 22 with T2 (56%) and 6 patients with T3 (16%). Prevalent were the tumors located in the lateral quadrants 17 (44%), followed by the centrally located tumors 12 (31%) and those in the medial quadrants 10 (25%). In 17 patients (44%) the histological type was invasive ductal carcinoma, followed by invasive lobular carcinoma, observed in 16 patients (41%) and other rare subtypes (in situ, ductal, lobular) in 6 patients (17%). Twenty-four patients (61%) had metastatic spread in the regional lymph nodes and in 3 (7%) the parasternal lymph nodes were engaged. In 20 patients (51%) the degree

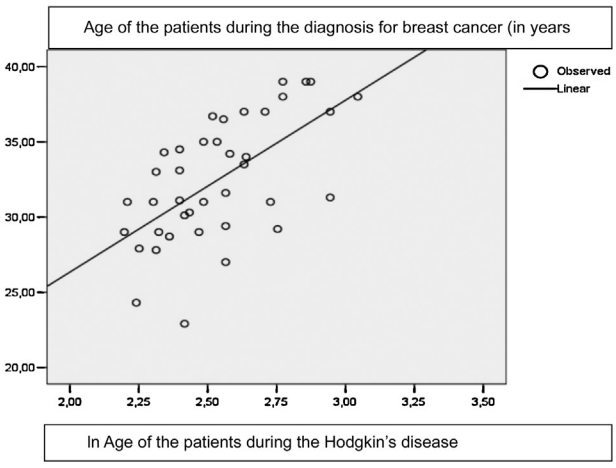

Fig. 1 – Scatter diagram.

of malignancy of the tumor was G3. Twenty-two women (56%) presented with positive receptor status, and 14 (36%) were HER2 (3+).

The median age at which the patients were diagnosed with the second malignancy – breast carcinoma was 32.4 years (22.9–39). The median time from treatment for HD to the diagnosis of BC was 17.7 years (11.7–24.3). The breast cancer patients were followed for a median period of 7.6 years (1–10). The survival which was observed was 95% for 5 year and 38% for 10 years.

The zero hypothesis was checked with a Chi-square test. According to this hypothesis in the population, from which the extract was made, there are no statistically significant differences in the tumor localization rates in the different quadrants of the beast. The Chi-square test demonstrated that the differences between the observed and expected rates were not statistically significant ($p = 0.207$).

In our analysis a significant correlation was found between the age at diagnosis of BC in years and the natural logarithm of the age at treatment for HD in years.

This relationship is illustrated by the scatter diagram shown in Fig. 1. The finding of significant linear correlation was the basis for the use of a linear regression analysis in which the following linear correlation was established:

$$\text{Age at diagnosis of BC (years)} = 3.481 + 11.429 \times \ln(\text{age at treatment for HD) (years)}$$

Based on this equation retrospective estimates of the age were made to assess how accurate such a prediction may be. Ninety-five percent confident intervals of the prognosis were found.

The results allowed for the use of the predictive equation when the age at treatment for HD (years) was in the range between 9 and 21 years.

4. Discussion

In recent years the risk factors associated with the development of radiation-induced breast cancer have been intensively studied. Convincing evidence has been accumulated for the significant role of age during radiation treatment for HD, the magnitude of the dose realized and radiation technique used. Radiation-induced tumors of the breast arise most commonly in the radiation field of the axillary and mediastinal lymph nodes, or at the border with the screened area on average 10–15 years after radiation therapy and continue to occur in the longest living patients.[9] This period corresponds to the long, multistep process of carcinogenesis, in which ionizing radiation is the main triggering factor. Despite reports that the carcinogenic effect of radiation is manifested between the fifth and ninth year, most solid tumors arise 10 years after radiotherapy and the risk of developing breast cancer is the highest after 15 years or more.[10–13] These data indicate the necessity of continued follow-up of patients with HD for early detection of second malignancies.

The relationship between the dose of irradiation and the risk for the occurrence of breast cancer has been investigated in large groups of patients with HD. A number of studies have found that external beam radiotherapy with a dose higher than 20 Gy, compared to a lower dose of 20 Gy, is associated with a significantly higher risk of developing breast cancer.[11] Techniques of radiation applied in the past, the so-called "mantle field" and especially the mandatory irradiation of axillary lymph nodes, are associated with an increased risk of developing radiation-induced breast cancer due to the lack of full protection of the mammary parenchyma.[14,15] Several studies have demonstrated a high incidence of bilateral breast carcinomas (21%) after radiotherapy of lymph chains above the diaphragm.[16,17] No correlation has been established between the dose of fractionation and the risk of development of secondary breast cancer.[9,18]

The importance of age at the time of irradiation for the onset of secondary breast cancer has been analyzed in a significant number of studies. There is certain evidence that irradiation at a young age is associated with a high risk of developing radiation-induced breast cancer in patients with HD. In the study of Hancock et al.[9] 1993 it has been found that the risk was the highest in patients irradiated at ages younger than 15 years – RR 136 (95% CI = 2.5–5.7). With increasing age, the risk for developing breast cancer declined, but remained significantly high in women who were irradiated under the age of 30 – RR 19 (95% CI = 10.3–32). Receiving radiation treatment above the age of 30 does not lead to an increased risk RR 0.7 (95% CI = 0.2–1.8).

Other authors have demonstrated higher risk for the development of secondary BC in patients who were treated at the age of 19, or younger compared to those treated in the age older than 19 years – RR 56 (95% CI = 23.7–107).[19] Follow up of 1380 children with HD aimed at determining the risk of occurrence of secondary neoplasms has shown that irradiation in childhood is associated with the highest risk for development of radiation-induced breast cancer.[8] Similar findings have been reported by Clemons et al.,[20] establishing that the highest risk of developing breast cancer is by irradiation between puberty and the age of 30.

Comparing the survival in 298 patients who have developed breast cancer after HD with 405 223 patients with only breast cancer, the authors report 5 years OS – 77%, 10 years OS – 59% and 15 years OS – 48% in the group BC after HD versus

5 years OS – 89%, 10 years OS – 72% and 15 years OS – 58% in the group of BC only $p \leq 0.00001$ CI (2.17–3.67).[21] The observed OS of the patients in our study was 95%, but statistically significant conclusion was difficult to be made, due to the low number of followed patients.

The question of the existence of clinical and pathological features that distinguish radiation-induced cancer from the spontaneously developed one is not fully understood. There are two published studies comparing the clinical and histological characteristics of secondary breast cancer that have developed in women treated for HD with a control group of women with spontaneously occurring carcinomas.[22–24] The results of the comparative analysis failed to demonstrate any differences in the survival of patients from both groups. This implies that radiation-induced cancers do not differ in clinical course and biological behavior from the spontaneously occurring cancers. Further studies on the problem are needed to prove or refute this statement.

The limited number of patients in our study does not allow for statistically valid conclusions, but these data show that radiation-induced tumors in young women tend to have a more frequent metastatic invasion in the regional lymph nodes, lateral localization, high degree of malignancy G3, as well as a predisposition for the development of distant metastases. This gives grounds to assume that the radiation-induced breast cancer developing in young adulthood has a more aggressive course and a worse prognosis.

The presented data suggest that patients treated for HD have a risk for developing radiation-induced BC, which is age-dependent. With the introduction of modern techniques for conducting radiation for HD, using linear accelerators, 3D conformal planning and treatment, a reduction in the dose to the breast parenchyma is expected as well as a decrease of the stochastic risk for a secondary malignant disease, including breast cancer. As a result of the introduction of more aggressive combined regimens of chemotherapy for HD, there has been a decrease in the overall dose of percutaneous radiotherapy, as well as a reduction in the irradiated volumes. There are ongoing trials in which after an evidence of full control of the HD on PET-CT, patients are left on dynamic control and do not receive radiotherapy. This therapeutic approach would reduce the risk of occurrence of breast cancer associated with radiation.

The statistical model has indicated that the equation for predicting the risk of developing BC following treatment for HD can be used when the age at treatment for HD is between 9 and 21 years.

5. Conclusion

Patients treated for HD, especially in their childhood and puberty need to be included in screening programs earlier than the accepted age limit of 25 years. In addition to the clinical examination, a mammography or ultrasound mammography is required.

Knowledge of the risk factors, biological features and clinical course of radiation-induced breast cancer will help to build an optimal regimen for the treatment of HD, which will help achieve the highest survival with minimal late toxicity.

Conflict of interest

None declared.

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