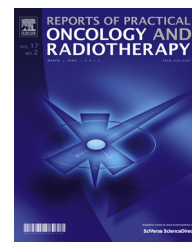


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## Original research article

# 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).<sup>1</sup> 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.<sup>2-4</sup> Acute nonlymphocytic leukemias, non-Hodgkin's lymphomas, breast and gastrointestinal carcinomas have been described.<sup>5-7</sup> 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.<sup>8</sup> 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;  $\chi^2$ -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%)
<b>T stage</b>	
pT1a	0 (0%)
pT1B	2 (5%)
pT1c	9 (23%)
pT2	22 (56%)
pT3	6 (16%)
<b>Histological type</b>	
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%)
<b>G</b>	
G1	6 (15%)
G2	13 (33%)
G3	20 (51%)
<b>LVI</b>	
LVI (-)	22 (56%)
LVI (+)	17 (2%)
<b>Hormonal status</b>	
ER, PR (+)	22 (56%)
ER, PR (-)	17 (44%)
<b>HER 2 status</b>	
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

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