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Breast Cancer after Hodgkin's Lymphoma: An Observational Study

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ABSTRACT

Background: Breast cancer (BC) counts for half of the excess risk of second cancer after Hodgkin Lymphoma (HL), but evidence about the clinical and pathological features of these cancers is lacking. The aim of this study was to evaluate whether these secondary BCs have distinctive characteristics compared to sporadic ones.

Methods: This is a case-control study comparing patients who developed BC after receiving treatment for HL with an age-matched cohort of non-irradiated patients. All the cases were treated at the Veneto Institute of Oncology (Padua, Italy) between 2002 and 2017. We analyzed the clinical and pathologic features of BCs and compared treatment modalities using Chi-squared tests. Kaplan-Meier survival analyses were conducted to investigate overall and disease-free survival in the two groups.

Results: In this study, 35 patients who were treated for HL and subsequently developed BCs were identified. BC occurred after a mean interval of 19.65 years (SD=10.08 years) from the HD diagnosis. According to the results, 4 of the patients treated for HL (11.4%) had a bilateral presentation. Also, 80% of the cases and 63% of the controls were ER+/HER- (p=0.516), while 20% of the HL group and 5.7% of the sporadic group were ER- /HER- (p=0.116). Ipsilateral BC recurrence (17.1% vs 8.6% in the sporadic BC group, p=0.346) and death events were more frequent in the HL group (11.4% vs 5.7% in the sporadic BC group, p=0.433), with a mean follow-up of 70 months (standard deviation=42.8months).

Conclusion: Our data show that BC arising after HL often presented with bilateral localization, aggressive biological profiles, and had high recurrence rates. Dedicated treatment modalities should be considered and evaluated in a multidisciplinary setting.

INTRODUCTION

Hodgkin's disease has achieved a remarkable 10-year survival rate exceeding 90%, since the introduction of radiotherapy (RT) and chemotherapy (CT) in the 1970s.[1] This accomplishment stands as a significant triumph in modern oncology[2], enabling the examination of the long-term effects of these treatments.[3] Compared with individuals in the general population, patients treated for Hodgkin lymphoma (HL) face an increased risk of developing secondary neoplasms compared to the general population.[4]

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Today, the emergence of secondary primary tumors is a major concern among long-term survivors. Breast cancer (BC) accounts for half of the elevated risk of developing a second cancer following Hodgkin's disease, as observed in a study by Shaapveld *et al.* in 2015.[5]

A comprehensive pooled analysis demonstrated an approximately nine-fold increase in the risk of secondary BC incidence (pooled RR = 8.23, 95% CI: 5.43-12.47, I^2 = 96%Ibrahim *et al.*[6]). The risk for these patients is among the highest ever reported for any population, and this is comparable to that of individuals carrying the BRCA1 gene mutation.[7] Notably, the risk is even higher when patients are irradiated at a young age with high-dose radiation. The average latency period for these secondary breast cancers is 10-20 years.[6] Although new therapeutic approaches for HL show promise in reducing the incidence of secondary cancers, this improvement has not yet been conclusively documented in clinical trials.[5]

Several hospital-based studies[8,9,10,11] have indicated that the clinical and pathological characteristics of these neoplasms may be more aggressive than those of sporadic cases, leading to a poorer prognosis. These distinctive characteristics are of particular interest as they can influence treatment choices.

Probably due to the rarity of the disease and the highly specific topic, only case series with a small number of patients investigated these characteristics, resulting in a lack of evidence in the literature.

Consequently, the indications for surgery and adjuvant therapies remain a subject of ongoing debate.

The primary objective of this study was to collect precise and useful evidence investigating whether BCs in patients with a previous history of HL exhibit unique characteristics compared to sporadic cases, with potential implications for treatment strategies and follow-up care.

METHODS

Study design and participants

This case-control study compares patients who developed BC following treatment for HL with an age-matched cohort of non-irradiated patients in a 1:1 ratio. All the cases were treated at the Veneto Institute of Oncology (Padua, Italy) between 2002 and 2017.After receiving approval from the Ethical Committee (Authorization Number: CET ANV: 2023-81), we conducted a comprehensive review of data from all the patients who developed BC after receiving treatment for HL during the study period. These data were extracted from the medical records of the Veneto Institute of Oncology (IOV-IRCCS) and data collection followed identical protocols in the two groups. To establish an age-matched control group without any significant risk factors for BC, we employed a random automatic selection process. This group comprised patients who had no history of prior irradiation and lacked known genetic mutations associated with BC. The selection process was limited to patients treated at the IOV-IRCCS during the same time frame (2002-2017). To limit the bias associated with changes in treatment strategies during the years and obtain comparable follow-ups, patients were also matched according to the year of diagnosis (+/- 2 years). The same assessment methods and follow up modalities were applied to both groups. While no formal sample size calculation was performed, we included all eligible patients who met the inclusion criteria.

We compared the clinical and pathological data, treatment modalities and follow-up approaches employed in both groups, aiming to provide a comprehensive account of the management of these patients. We excluded individuals with ductal carcinoma in situ and those who were carriers of known genetic mutations that predispose them to BC.

Collected data

We systematically gathered a wide range of information including familial history, physiological and pathological medical history, details regarding the age at diagnosis, neoadjuvant and adjuvant therapies administered for HL and BC, as well as pathological findings derived from surgical specimens. Additionally, we documented instances of BC recurrence, and the subsequent treatments provided. These data were recorded and continually updated in a database maintained by our research team.

These records were drawn from the clinical documentation and other pertinent sources. We applied the American Joint Committee on Cancer's (AJCC) seventh edition TNM staging system for staging. To simplify the evaluation, we categorized BC events as either "node positive" (indicating at least one positive lymph node in the definitive histological examination) or "node negative." Data for the control group were collected using the same standardized methods and were similarly entered into our database. We also compiled comprehensive information regarding HL, which encompassed details such as histological subtypes, age at diagnosis, the type of treatment employed, and the stage of the disease.

Follow-up data

Our study defined the end of the follow-up period as the last recorded interaction with our institute,

which could include the patient's last visit to surgeons, oncologists, or radiation therapists, the final radiological examinations conducted, or in cases where applicable, the patient's date of death. In most cases, the patients' follow-up assessments took place at our institute, allowing for the evaluation of clinical data through the consultation of the IOV - IRCCS clinical records. For those patients who had their follow-up assessments conducted at other healthcare facilities, telephone contact was used to obtain the necessary information. Furthermore, we measured the latency period as the time elapsed between the two diagnoses, enabling us to understand the duration between the diagnosis of HL and the subsequent diagnosis of BC. This information was crucial in assessing the potential link and the timing of these two conditions in our study.

As the risk of developing BC is greatest when patients are irradiated at young age[6] and this may be related to a different mechanism of carcinogenesis than sporadic BC, there is some research suggesting that latency and age of HL diagnoses may impact the post-radiation therapy BCs subtypes.[11] Moreover, also the prior use of CT and its related menopause may alter the biological profile of BC. A dedicated analysis was performed to evaluate if the variation of these 3 risk modifying factors (namely latency, age of HL diagnoses and previous treatments) may suggest some distinctive distribution of the clinical-pathological features, the distributions of grading, proliferation index, vascular invasion, lymph node status and luminal profile.

Statistical analysis

Qualitative variables were presented as absolute values and percentages. In the case of quantitative variables, we expressed them in terms of the mean and standard deviation (SD) or median and inter-quartile ranges depending on the normality of distributions. To explore the relationships between all the relevant clinical and pathological features (namely grading, proliferation index, vascular invasion, axillary lymph nodes status, luminal profile and histological type) and the primary predictors (such as the age of HL's diagnosis, type of treatment, and latency), we employed Chi squared tests. We utilized the Log-Rank test to compare survival curves, which helped us assess any differences in survival rates among the studied groups or cohorts. Overall survival (OS) was described according to the time between the BC diagnoses to death, while disease free survival (DFS) was defined considering the time from BC diagnoses to the first local or distant recurrence. Statistically significant P-values were considered when they were less than 0.05, and the analysis was carried out with a statistical power of 80% to ensure the reliability of our findings. We conducted our statistical analysis using STATA 11.0 software.

RESULTS

Thirty-five patients were treated for secondary BC after HL at IOV - IRCCS between 2012 and 2017. The sporadic cohort was created by including age-matched patients surgically treated for BC at our institution during the same period. All 70 patients were females living in Italy, most of whom were white Caucasians. The mean latency between the HL and BC diagnoses was 19.65 years (standard deviation (SD)= 10.8 years).

Table 1. Histopathological characteristics of breast cancer arising after Hodgkin lymphoma and of sporadic breast cancer

Variables	Sporadic BC (n=35)	BC post HL (n=35)	P value
Mean age (years)*	49.3	48.9	0.872
Stage			0.279
IA	25 (71.4%)	21 (60%)	
IB	0	3 (8.3%)	
IIA	7 (20%)	5 (14.3%)	
IIB	1 (2.9%)	4 (11.4%)	
IIIA	1 (2.9%)	1 (2.9%)	
IIIC	1 (2.9%)	0	
NA	0	1 (2.9%)	
Grade			0.271
G1	9 (25.7%)	6 (17.1%)	
G2	11 (31.4%)	13 (37.1%)	
G3	15 (42.9%)	13 (37.1%)	
NA	0	3 (8.6%)	
Positive lymph node(s)	29 (82.9%)	26 (74.3%)	0.382
No	6 (17.1%)	9 (25.7%)	
Yes			
Histopathology			0.356
IC NST	31 (88.6%)	29 (82.9%)	
ILC	3 (8.6%)	6 (17.1%)	
Mixed	1 (2.9%)	0	
Vascular invasion			0.109
No	29 (82.9%)	22 (62.9%)	
Yes	6 (17.1%)	11 (31.4%)	
NA	0 (0%)	2 (5.7%)	
MIB-1			0.811
< 20%	18 (51.4%)	19 (54.3%)	
> 20%	17 (48.6%)	16 (45.7%)	
HER2 expression			0.743
Negative	30 (85.7%)	29 (82.9%)	
Positive	5 (14.3%)	6 (17.1%)	
Luminal subtypes			0.280
	28 (80%)	22 (62.9%)	
ER+/HER2-	4 (11.4%)	4 (11.4%)	
ER+/HER2+	1 (2.9%)	2 (5.7%)	
ER-/ HER2+	2 (5.7%)	7 (20%)	
TN			

LEGEND: Chi squared or Fisher exact tests; *Wilcoxon test

The mean age at diagnosis for BC was 49 years in both groups (SD=9.9 years). The BC diagnoses were made between 2002 and 2017, with 91.4% of them being made between 2007 and 2017.

The histopathological characteristics of BC arising after HL and of sporadic BC are shown in Table 1.

No significant differences in terms of clinical and pathological findings were observed between the 2 groups. Overall, 68.3% of all the BC patients after HL were diagnosed at stage IA or IB. The most common histological subtype was non-special type (83%), and 63% of the neoplasms were ER+/HER2-. ER-/HER2- BC was more common in patients with prior diagnosis of HL than in their counterparts (20 vs. 5.7%, p=0.116), although the global luminal subtypes distribution analysis demonstrated non-significant differences. Vascular invasion was more frequent in the post-HL group than in the sporadic group (31.4 vs 17.1%, P=0.109). Four patients treated for HL (11.4%) had a bilateral presentation. There were one synchronous presentation and three metachronous presentations. The metachronous cases presented 1, 4, and 18 years after the first presentation, respectively. All the bilateral presentations were treated with bilateral mastectomy. Most of the patients with bilateral presentation were irradiated before the age of 30 years. None of the patients in the control group had a bilateral presentation.

The surgical treatment modalities were similar in the two groups, except for the laterality. Six of the BCs after HL were treated with bilateral mastectomy (one case because of synchronous bilateral presentation and five with contralateral prophylactic mastectomy).

According to the multidisciplinary meeting decisions, adjuvant therapies for patients with BC after HL were distributed as follows: 11 received adjuvant RT, 4 were given anti-Her2 therapies, adjuvant chemotherapy was administered to 20 patients and 24 patients underwent hormone-therapy.

The mean follow-up time was similar in the 2 groups (70.7 months in the after-HL group (SD= 55.7 months) and 69.9 months (SD= 30.0 months) in the sporadic BC group, P=0.555). The rates of recurrence and death are reported in Table 2, while the survival curves are illustrated in Figure 1.

The comparison of survival curves (Logrank test) demonstrated non-significant differences (P=0.393 for OS, p=0.753 for DFS). Also, the 5-year OS was 97.1% (standard error (SE)= 0.023) in the sporadic BC group and 88.5% (SE= 0.064) in the BC post HL group, with the 5-year DFS being 96.4% (SE= 0.035) in the controls and 90.9% (SE=0.062) in the cases.

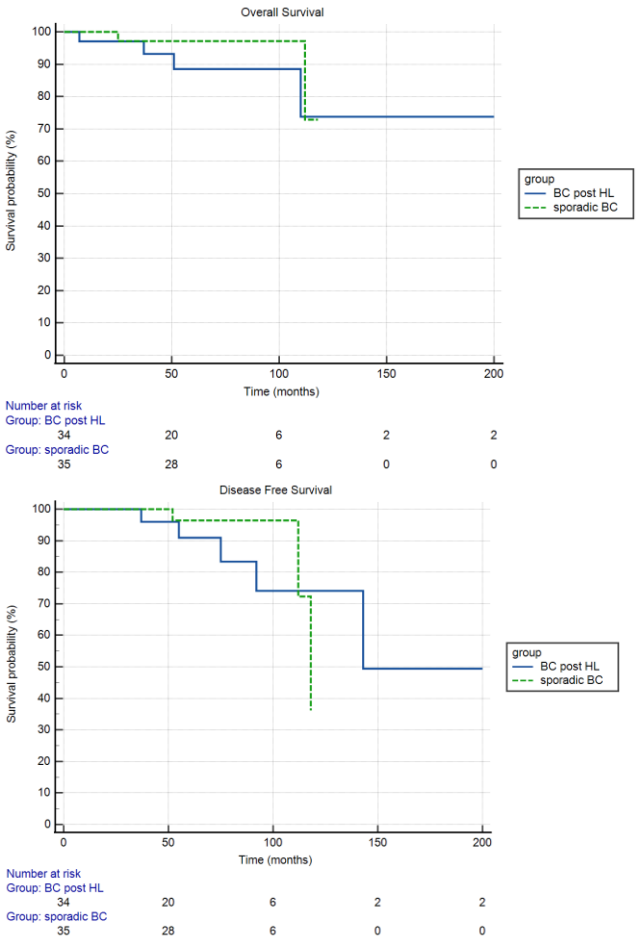

Figure 1. Kaplan Meyer analyses on survival outcomes in the two populations

Table 2. Surgical, recurrence and mortality outcomes of breast cancer arising after Hodgkin lymphoma and of sporadic breast cancer.

Variables	Sporadic BC (n=35)	BC post HL (n=35)	P value
Type of surgical approach			1.000
Wide local excision	23 (65.7%)	23 (65.7%)	
Mastectomy	12 (34.3%)	12 (34.3%)	
Recurrence of disease			0.284
No	32 (91.4%)	29 (82.9%)	
Yes	3 (8.6%)	6 (17.1%)	
Death			0.393
No	33 (94.3%)	31 (88.6%)	
Yes	2 (5.7%)	4 (11.4%)	

LEGEND: Chi squared test

The number of events of ipsilateral BC recurrence was greater in the HL group, although a significant difference between the two groups was not observed (8.6% vs 17.1%, P=0.284). Three of these cases of ipsilateral BC recurrence occurred during the first 5 years of the follow-up, while the other 3 happened

between 5 and 10 years after the first BC diagnosis. Finally, 4 death events were observed in the case group, and 2 of these patients had BC metastasis (P=0.394).

Characteristics of HL patients who subsequently developed BC

Hodgkin lymphoma diagnoses were made between 1963 and 2017, with 15 patients being diagnosed between 1990 and 2000, 13 before 1990, and 7 after 2000. The most common type of lymphoma was classic, with sclero-nodular type being the most common variant.

The mean age at HL diagnosis was 28.57 years (SD= 10 years).

All patients were irradiated with radiation fields involving the mammary gland. Most of the patients were irradiated using the mantle irradiation technique (93% of all patients). Radiation doses varied between 20 Gy in 10 fractions to 40 Gy in 20 fractions.

Chemotherapy was used in 25 cases (71%), with 22 patients treated with adriamycin, bleomycin, and vinblastine sulfate (ABVD) protocol, and 3 patients with the Standard V protocol. Three of them also underwent splenectomy (those patients were treated before 1990).

Distributions of clinical and pathological characteristics in differences regarding known risk modifying factors

No significant variation in the characteristics' distribution was observed considering latencies <20 or >20 years. Results are shown in Table 1S (supplementary material).

Moreover, the distributions of pathological findings did not show statistically significant differences according to the type of treatment for HL, but it can be observed that the ER+/HER2- and the ER-/HER2+ profiles were more frequent if CT was associated with RT (68 vs 50%, P=0.629 and 8 vs 0% P=0.383 of the cases, respectively), as illustrated in Table 2S (supplementary material).

There were no statistically significant variations in terms of distribution of pathological characteristics regarding the differences in age at HL diagnosis, except for the histotype. Lobular invasive BC was more frequent in patients irradiated for HL after the age of 30 years, compared to patients treated for HL before 30 years (5 vs 1 cases, P=0.028), as showed in Table 3S (supplementary material).

BC mean age at diagnosis was 46.3 years if HL diagnosis occurred before the age of 30 years and 52.3 years if the patients were treated for HL after the age of 30 years. Mean latency of patients treated for HL before the age of 30 years was 23.7 years, while it was equal to 14.6 years in patients treated after the age of 30 years.

DISCUSSION

This study compassed the experience of the Veneto Institute of Oncology in managing BC arising after treatments for HL. It provides a comprehensive description of the clinical management of this relatively rare yet distinctive secondary neoplasm. In this relatively small population, there were no statistically significant differences in the distribution of pathological findings in BC occurring after HL compared to an age-matched group of patients with sporadic BC. However, the HL group exhibited a high prevalence of the ER-/HER- profile, bilateral BCs, ipsilateral recurrences, and early age clinical presentation, suggesting a potentially aggressive biological behavior. This underscores the importance of exercising particular caution when evaluating treatment strategies for these patients. In the absence of randomized and multicentric studies on this population, these results provide crucial data that may contribute to defining surveillance, treatment, and follow-up strategies for individuals at elevated risk of BC due to prior HL.

Clinical and pathological features of BC arising after HL

In the literature, small monocentric studies have described differences in terms of immunohistochemical distributions between HL and sporadic BC populations. Dores *et al.*[4] demonstrated that the risk of developing ER-/PR- neoplasia is 9 times higher for BC after HL than for BC compared to an age-matched series of BC in the general population. Horst *et al.*[11] reported that BC after HL is more often ER-/HER2- than sporadic BC (39% in 51 BC after HD, 14% in an age-matched sporadic BC group). Our data showed that ER-/HER- status was more common in the HL group (20 vs 5,7%) and ER-/PR- was more frequent in BC arising after the treatments for HL (25,7% vs 8,6%), but the differences were not statistically significant.

The results of a monocentric case series of radio-induced BC[4,12] indicate that the stage distribution of radiation-related BC is similar to that of sporadic BC. This is consistent with our findings and may be related to the special surveillance protocols used for these patients.

The type of treatment for HL may influence the distributions of the histological findings of BC. Indeed, irradiation may affect the number of bilateral presentations, consistent with the concept of field carcinogenesis. Our study demonstrated that this has repercussions in clinical practice, since we observed a notable difference (6 in HL vs 0 in sporadic BC

group) in bilateral presentations between the 2 groups. This report finds confirmations in the literature: Yahalom *et al.*[8] reported 8 bilateral BC presentations in 37 patients (22%). This should be evaluated when considering the treatment choice, and some authors[13] have described prophylactic contralateral mastectomies as valid strategies to lower the likelihood of bilateral metachronous events.

Radiation-induced BC appears to occur in women younger than BC in the general population. A meta-analysis by Ibrahim *et al.*[6] found that the mean age at diagnosis of BC after HL was 35 years, based on the data of 957 incidences of SBC in 34 studies. This suggests that the patients treated with radiation at a young age deserve a dedicated follow-up, starting before the general population. In our population, the mean age at diagnosis was 48,9 years and the global range was 32-74 years.

As described by Castiglioni *et al.*[12] for a small cohort of patients treated with radiation therapy for HL or other pediatric solid tumors population, the HER2 + subtype is more frequent in women irradiated during the pre-menarche period compared to a sporadic BC population. Radiation administered to the chest during breast maturation may be a risk factor for HER2 overexpression in BC, as it could trigger chromosomal instability and result in amplification of the erbB2 gene. In our group, only 6 of the irradiated patients showed amplification of HER2, but we could observe that they were diagnosed with HL at young ages (20% if the diagnosis was<30 years, 13.3 % if the diagnosis of HL was >30 years). Broeks *et al.*[14] conducted a gene expression profiling study demonstrating that the HER+ BC in patients with prior diagnoses of BC is more frequent in patients who were irradiated at a young age. In our study the immunohistochemical surrogate profile was rare, but the mean age at irradiation was similar to the one described by Broeks *et al.* (equal to 22 years), suggesting a possible different mechanism of carcinogens for the patients irradiated at a young age.

Surveillance, treatment and follow-up strategies for BC arising after HL

The choice of the correct therapeutic approach for these patients is still controversial. At our institution, the treatment modalities used in the 2 groups were similar.

Traditionally, RT in a previously irradiated chest was avoided, so in recent decades mastectomy has been offered to these patients as the gold standard. The results of recently published studies[15,16] demonstrated that reirradiation for ipsilateral BC recurrence does not increase the rate of complications. By extracting data from the Surveillance, Epidemiology, and End Results database, Burt *et al.*[17] concluded that breast conserving therapy did not have an inferior cancer specific survival (CSS) or overall survival (OS) compared to other treatment modalities for female HL survivors who subsequently developed BC. Therefore, nowadays a conservative treatment could be acceptable even for BC arising after HL.[17] The dose of prior RT (linear relationship between dose and risk of BC), age of treatment and latency may help us to select which patients may avoid mastectomy. Additionally, prior use of CT should be considered (for example, the use of anthracyclines may lead to a higher risk of BC while procarbazine is associated with a lower risk, probably because of gonadotoxicities[18,19]). Moreover, intraoperative RT (TARGIT-IORT) could be a reasonable option to minimize the post-RT toxicities in these populations.[20]

The use of contralateral prophylactic mastectomy (CPM) may still have a rationale for some patients, given the elevated risk for BC and the fact that symmetry is easier to achieve when mastectomies are bilateral. The Contralateral Prophylactic Mastectomy Consensus Statement from the American Society of Breast Surgeons[13] described patients who were irradiated at a young age as perfect candidates for CPM. In our case series, none of the 6 bilateral mastectomies had surgical complications. The results of a metanalysis[6] show that the younger is the age at irradiation, the higher is the risk for BC. The choice of treatment modality should take into consideration: the age of treatment for HL, other treatment modalities, familiarity, and genetic predisposition.

Due to the rarity of the pathology and ethical issues, it is difficult to perform randomized clinical trials, so other retrospective and prospective studies will hopefully provide evidence for guiding the best therapeutic choices for the patients.

In our cohort, small numbers of recurrence and death events were observed, but patients with BC after HL were more likely to have local or contralateral BC recurrencies, and death events were more frequent. Regarding prognosis, the literature shows evidence from monocentric studies with conflicting data: while the overall survival (OS) is lower (also because of cardiac and pulmonary comorbidities), the BC specific survival (CSS) seems to be similar to that of sporadic BC[17]). A study by Moskowitz *et al.*[7] demonstrated that mortality after BC was higher in childhood cancer survivors than in women with de novo BC. Some authors have proposed that undertreatment of these patients is a cause of worst OS and CSS.[21] Therapeutic options may be limited because of prior administration of RT or CT agents such as anthracyclines.

These patients should undergo a specific and extensive follow-up, but the literature describes low awareness levels and indicates that the specific follow-up is often not offered or not performed.[22] Initiation of surveillance for BC with mammography and MRI is recommended at age 25 years or ≥ 8 years from radiation for female survivors who are children, adolescents and young adults (CAYA) treated with ≥ 10 Gy chest radiation and should last up to 60 years of age.[23] Thus, awareness is a major concern for this population.

This study has several limitations, starting from its retrospective nature. The Veneto Institute of Oncology is also a reference center for radiotherapy, so most of the patients with BC arising after HL were treated for the two neoplasia in our center. However, some of the patients were treated at IOV – IRCSS only for BC, so data about specific protocols about RT for HL were not available for a limited number of patients. Another limitation is the lack of information regarding post operative complications and post-therapy toxicities (such as shoulder-arm morbidity and lung or heart adverse outcomes). The number of BCs after HL was low, partly because our study is mono-institutional, and partly because of the rarity of the pathology, despite the high relative risk for this population. HL diagnoses were made decades ago, when HL treatment modalities were very different from current practice. Historically, RT was extensively used in the HL treatment protocols, but recent strategies have minimized its use, favoring CT over RT and limiting RT indications, with RT often omitted in favorable HL. However, we believe that, considering the decades of latency, the results of this study are still of current interest, because these are the cohorts of patients who are currently being treated for BC. Moreover, the rate of secondary BC is still elevated, even in cohorts of HL patients with lower radiation exposure.[5]

CONCLUSION

This study revealed no statistically significant differences in the distribution of pathological findings between patients with BC occurring after HL and patients with sporadic BC in an age-matched group. However, BC arising after HL is often bilateral and triple negative; moreover, it tends to have more frequent local recurrence than sporadic BC. Therefore, dedicated surveillance, treatment and follow up modalities need to be considered. Awareness is fundamental in this group of patients. While BCT may be an acceptable treatment option for selected groups of HL survivors diagnosed with BC, patients who are irradiated with high doses and bilateral fields at a young age may still be good candidates for contralateral prophylactic mastectomy. Factors like the age at irradiation, the dose and types of radiation therapy, the use of CT and other treatment modalities, familiarity, patient preferences, and genetic predisposition must be taken into consideration when considering treatment choices. While more robust evidence is hopefully needed, the gold standard approach for these patients is still controversial, and decisions should be made in a multidisciplinary setting.

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None.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ETHICAL CONSIDERATIONS

Approval from the Ethical Committee (Authorization Number: CET ANV: 2023-81) was obtained.

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DATA AVAILABILITY

All relevant data are within the paper and its supporting information files. Anything else needed is available upon request.

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