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Breast cancer occurred after Hodgkin's disease: Clinico-pathological features, treatments and outcome: Analysis of 214 cases

Bruno Cutuli[a,*], Samia Kanoun[b], Christine Tunon De Lara[c], Marc Baron[d], Lorenzo Livi[e], Cristelle Levy[f], Christine Cohen-Solal-Lenir[g], Anne Lesur[h], Pierre Kerbrat[i], Mariano Provencio[j], Laurence Gonzague-Casabianca[k], Alice Mege[l], Claire Lemanski[m], Catherine Delva[n], Sylvie Lancrenon[n], Michel Velten[o]

[a] *Radiation Oncology Department, Polyclinique de Courlancy, 38 rue de Courlancy, 51100 Reims, France*
[b] *Institut Gustave Roussy, Villejuif, France*
[c] *Institut Bergonié, Bordeaux, France*
[d] *Centre Henri Becquerel, Rouen, France*
[e] *Universita di Firenze, Florence, Italy*
[f] *Centre Henri Baclesse, Caen, France*
[g] *Centre Rene Huguenin, Saint Cloud, France*
[h] *Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France*
[i] *Centre Eugene Marquis, Rennes, France*
[j] *Hopital Puerta de Hierro, Madrid, Spain*
[k] *Institut Paoli-Calmettes, Marseille, France*
[l] *Institut Sainte-Catherine, Avignon, France*
[m] *Centre Val d'Aurelle, Montpellier, France*
[n] *Sylia-Stat, Bourg-la-Reine, France*
[o] *Centre Paul Strauss, Strasbourg, France*

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* Corresponding author. Tel.: +33 3 26 84 02 84; fax: +33 3 26 84 70 20.
E-mail addresses: bcutuli@iccreims.fr, diane.penet@orange.fr (B. Cutuli).

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Abstract

Background: Secondary tumours (ST) represent a major concern in survivors of Hodgkin's disease (HD). Breast cancer (BC) is the most frequent ST among young treated women.

Material and methods: One hundred and eighty-nine women treated for HD by radiotherapy (RT) and/or chemotherapy (CT) subsequently developed 214 BCs.

Results: Median age at HD diagnosis was 25 years (34% were less than 20). Median interval between HD and BC was 18.6 years, with a 42-year median age at first BC. According to the TNM classification, there were 30 (14%) T_0 (non palbable lesions), 86 (40%) T_1, 56 (26%) T_2, 13 (6%) T_3T_4 and 29 (14%) T_x. There were 25 (13.2%) contralateral BC. 160 (75%) and 15 (7%) tumours were infiltrating ductal and lobular carcinomas, 7 (3.3%) were other subtypes and 27 (22%) DCIS.

The rate of axillary nodal involvement was 32%. Among 203 operated tumours, 79 (39%) were treated by breast conserving surgery (BCS), with RT in 56 (71%) cases. CT and hormonal treatment were delivered in 51% and 45% of the patients. With a 50-month median follow-up, local recurrence occurred in 12% of the tumours (9% after mastectomy, 21% after lumpectomy alone and 13.7% after lumpectomy with RT). Metastasis occurred in 47 (26%) patients. The risk factors were pN+, pT, high SBR grade and young age (<50 years). The ten-year overall and specific survival rates were 53% and 63.5%, respectively. The ten-year specific survival rates were 79% for $pT_0T_1T_2$, 48% for pT_3T_4 ($p = 0.0002$) and 79% for pN_0 versus 38.5% for pN+ ($p = 0.00026$). Among 67 deaths, 43 (73%) were due to BC.

Conclusion: Patients and physicians should be aware that BC is the most frequent secondary tumour in young women treated for HD. The new RT modalities (lower doses and involved fields) may decrease the risk in the future. However, these women require a careful monitoring as from 8 to 10 years after HD treatment, combining mammography, ultrasound and MRI according to several ongoing studies. BC with whole breast irradiation is feasible in some selected cases.

Keywords: Breast cancer; Hodgkin's disease; Secondary cancers; Radio-induced cancers; Breast conserving treatment; Thoracic irradiation; Ductal carcinoma in situ

1. Introduction

Until the 50s, Hodgkin's disease (HD) was a permanent fatal disease. In the 60s, radiotherapy (RT) and chemotherapy (CT) radically changed prognosis, especially using large field irradiations and polychemotherapies. However, after such treatments, several long-term side-effects were observed and the occurrence of second primary cancers still remains the most important [1–4].

Many reports have confirmed a significant increased risk of secondary acute non-lymphocytic leukaemia (ANLL), non-Hodgkin's lymphoma (NHL) and solid tumours (ST) among HD long-term survivors [5–7].

Breast cancer (BC) is the most frequent ST occurring in women treated for HD [8–17]. The "latency interval" is quite long, i.e. approximately 15 years, and the risk dramatically increases in young girls and adolescents until 20–25 years old. Several reports have brought data on BC incidence among large cohorts of women treated for HD, but relatively few data are available on the clinico-pathological characteristics, treatment modalities (especially possible treatment by breast conserving therapy including whole breast irradiation) and more particularly outcome in patients with secondary BC.

Thus, after a previous study published in 2001 [18], we performed a new retrospective and multicentric review to assess the specific histopathological features, locoregional and systemic treatments as well as prognostic factors of such secondary BC. Finally, we tried to suggest preventive actions by specific screening and/or chemoprevention.

2. Material and methods

In a retrospective international study performed in 14 hospitals, private clinics and cancer centres, 189 women treated for HD who subsequently developed a total of 214 BCs were found. The clinical and histological data for BC were almost fully obtained. However, several parameters for HD were not exhaustive (stage/treatment details), especially in older cases (45% of the cases with an over 20-year interval between HD and BC) and for some of the patients treated for HD elsewhere and further referred to one of the 14 centres only after BC diagnosis. To our knowledge, this study describes the largest series on detailed clinical and histological features of BC occurring after HD treatment.

2.1. Statistics

The analysis was performed using the Kaplan–Meier method for disease-specific survival. Deaths of patients with no evidence of BC and from causes not related to BC were censored in the product-limit calculation of specific survival. The Mantel–Cox (log-rank) test was used to compare survival curves.

3. Results

3.1. HD clinico-pathological features and treatments

The median age at diagnosis of HD was 25 years (range 7–67 years). Globally, 47 women (34.4%) were 20 years old

Table 1
Clinico-pathological features for Hodgkin's disease (HD). Analysis of 189 patients.

	%
Treatment period	
<1970	17
1970–1980	38
1981–1990	34
>1990	11
Age at diagnosis	
<20 years	25
20–30 years	45
>30 years	30
Ann Arbor stage ($n = 169$)	
I	22
II	56
III	16
IV	6
Histology ($n = 133$)	
Lymphocyte predominance	9
Nodular sclerosis	63
Mixed cellularity	23
Lymphocyte depletion	5
Treatment ($n = 185$)	
RT alone	28
CT alone	2.7
RT + CT	69.3
RT technique ($n = 182$)	
Mantle	79
Involved fields	21
Supradiaphragmatic RT doses (Gy)	
<36	7
39–40	66
>40	27

or less and three were young girls (7, 8 and 9 years old). Main clinico-pathological features of HD were detailed in Table 1. One hundred and eighty-two patients underwent radiotherapy (RT): alone in 28% of the cases and associated with chemotherapy (CT) in 69%. All patients received supradiaphragmatic RT, mainly by classical mantle (extended) field. The X-ray energies used were: cobalt photons: 79, 6–10 X megavolts: 27, 15–25 megavolts: 35 and not specified: 41. Fifty-eight patients (34%) underwent splenectomy and 54 subdiaphragmatic irradiation. Only 5 women (2.6%) were treated exclusively by CT, whereas 128 (69%) underwent CT and RT. MOPP protocol was used in 57 patients, ABVD in 17 and a MOPP-ABVD combination in 25; 29 patients were treated by other combinations, mainly based on vinblastine. The median number of delivered cycles was 6. Twenty-one (11%) women relapsed after various time intervals; three were treated by RT alone, 10 by CT alone and 8 by both modalities.

3.2. Breast cancer: clinical characteristics

The median interval after HD treatment and BC occurrence was 18.6 years (range 2–50 years), with no significant differences according to initial HD treatment: RT alone: 17 years, CT + RT: 19 years. BC occurred after HD diagnosis within 10 years, between 10 and 20 years and after 20 years in 9.6%, 45.4% and 45% of the cases, respectively. Median age at diagnosis of the first BC was 42 years.

According to TNM classification, we found (all cases included) 30 (14%) T_0 (non palpable lesions), 86 (40.1%) T_1, 56 (26.2%) T_2, 13 (6%) T_3T_4 and 29 (13.6%) T_x. There were 25 contralateral BC (13.2%), of which 3 synchronous and 22 metachronous.

Thirty-six (19%) tumours were multifocal. Six (3.2%) patients had metastases at first diagnosis.

3.3. Breast cancer: histopathological features

160 (74.7%) tumours were infiltrating ductal carcinomas (IDC), 15 (7%) were infiltrating lobular carcinomas (ILC), 7 (3.3%) were other infiltrating subtypes and 27 (21.6%) were ductal carcinomas in situ (DCIS). Five cases were not specified.

Among 164 out of 187 evaluable infiltrating carcinomas, 30 (18%) were SBR I (Scarff-Bloom-Richardson histoprognostic grade), 70 (43%) were SBR II and 64 (39%) were SBR III.

Among 149 evaluable tumours, estrogen (ER) and progestin (PgR) receptors were positive in 58.4% and 51.4% of the cases, respectively (with a global ER and/or PgR positivity rate of 65%). Her2 overexpression was found in 5 out of 41 (21%) IBC treated after 2001. Among 168 infiltrating carcinomas for which axillary dissection was performed, 115 (68%) had no axillary involvement (pN_0), 37 (22%) had 1– 3 involved nodes (pN_1) and 13 (8%) had more than 3 involved nodes ($pN_{2–3}$). In three cases (2%), the number of involved nodes was not specified.

3.4. Breast cancer: treatment

Four metastatic patients and another two with advanced lesions (T_4N_1) only received medical treatment. Among 203 operated tumours, 79 (39%) were treated by lumpectomy or quadrantectomy (8/27 (29.6%) DCIS and 71/176 (40.3%) infiltrating carcinomas) and 124 (61%) by mastectomy. Axillary dissection was performed in 168 out of 187 cases.

After conservative surgery, whole breast irradiation was delivered in 56 out of 79 (71%) cases: 5/8 (62%) in DCIS and 51/71 (72%) in infiltrating carcinomas.

After mastectomy, radiotherapy was delivered only in 11 out of 121 (9%) cases. Chemotherapy (CT) was delivered in 95 out of 187 (51%) patients with infiltrating carcinoma (associated with Trastuzumab in five cases). Hormonal treatment (HT) was used in 93 cases (45%). CT and HT were both strongly influenced by axillary nodal status and age (Table 2).

3.5. Outcome

3.5.1. Locoregional recurrences

With a 50-month median follow-up, twenty-five (12%) out of 210 evaluable tumours underwent local recurrence: 3 out

Table 2
Influence of axillary nodal status and age on chemotherapy (CT) and hormonal treatment (HT) use.

	CT use (%)	*p*	HT use (%)	*p*
Axillary nodal status				
pN_0	37		45	
pN_{1-3}	81	<0.0001	46	0.26
$pN_{>3}$	84.6		69	
Age				
≤50 years	59.5	0.0041	37	0.0005
>50 years	37.7		654	

of 26 (11.5%) among DCIS and 22 out of 184 (12%) among invasive tumours.

Among invasive tumours treated by conservative surgery alone, 4 out of 19 (21%) relapsed, compared to 7 out of 51 (13.7%) when radiotherapy was added.

Nine out of 100 (9%) patients treated by mastectomy relapsed. On the other hand, one out of three DCIS treated by conservative surgery alone relapsed, whereas there were no LR among four DCIS treated with RT. There were two LR among 18 DCIS treated by mastectomy.

Six nodal recurrences were reported: two in the axilla, two in the supra-clavicular fossa, one in the internal mammary chain and one without specified topography.

3.5.2. Metastases

Six patients were metastatic at time of diagnosis. Among 183 patients with initial localized disease, 47 (27%) further developed metastasis. The metastatic risk was much higher in women with BC diagnosis under 50 than in older ones (37% versus 15.7%, $p = 0.0061$), and was significantly influenced by pT status (17.5% for pT_0–T_1 versus 50% for $pT_2T_3T_4$, $p < 0.0001$), pN status (19.2% for pN_0 versus 52.2% for pN+) ($p = 0.0001$) and SBR grading (II–III versus I, 36.2%, $p = 0.0022$), whereas hormone receptor status and HD-BC delay did not (Table 3).

Table 3
Metastatic risk factors (univariate analysis).

	Metastases		
	n	%	*p*
pT			
$pT_0 - pT_1$	17/97	17.5	
pT_2	27/5	51.9	<0.0001
$pT_3 - pT_4$	2/6	33.3	
pN			
pN_0	19/99	19.2	
pN_{1-3}	13/34	38.2	<0.0001
$pN_{>3}$	11/12	91.7	
SBR			
I	0/23		
II	21/62	33.9	0.0022
III	21/54	38.9	
Age			
<50 years	39/105	37	
≤50 years	8/51	15.7	0.0061
Delay HD-BC			
<10 years	5/14	35.7	
10–20	20/75	26.7	NS
>20 years	22/67	32.8	

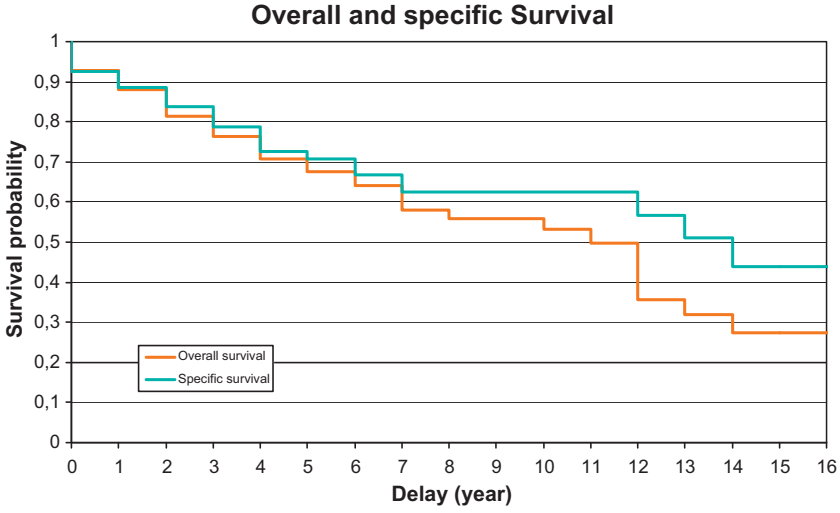

Fig. 1. Overall (OS) and disease specific survival (DSS) rates.

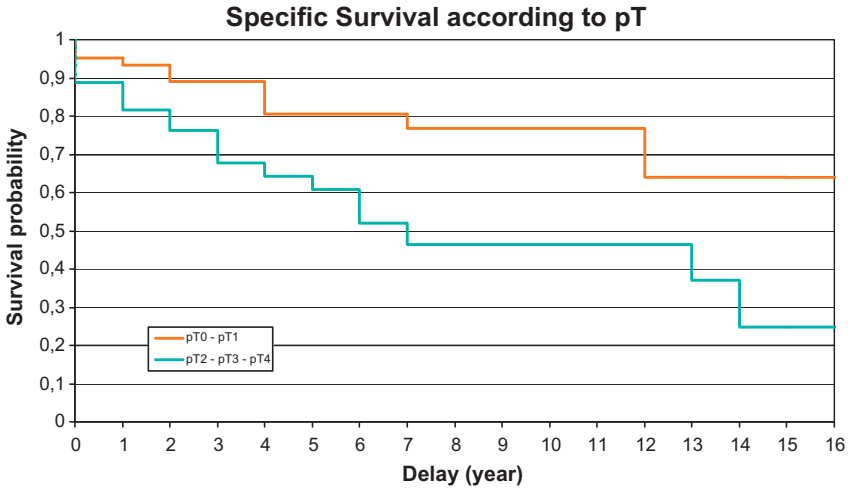

Fig. 2. Disease specific survival (DSS) rates according to pT.

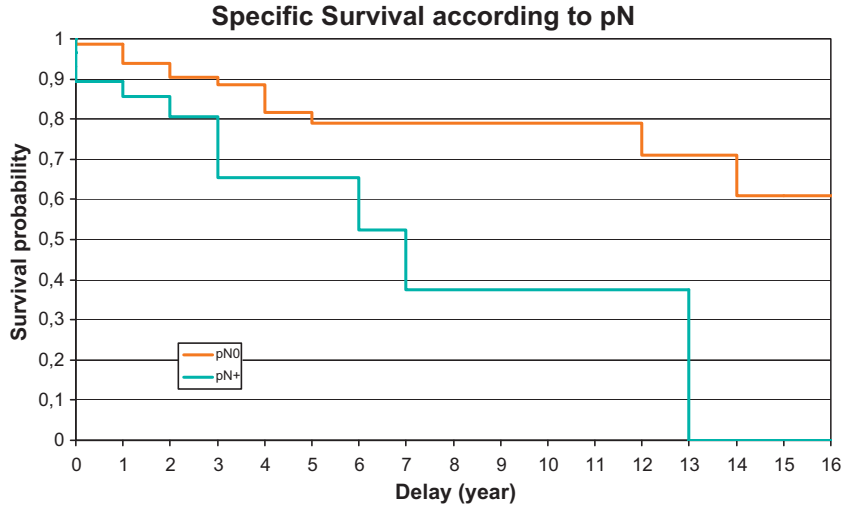

Fig. 3. Disease specific survival (DSS) rates according to pN.

3.5.3. Overall and disease-specific survival rates

The overall 5- and 10-year survival rates were 69.8% and 52.7%. The corresponding breast cancer specific rates were 72% and 63.5% (Fig. 1).

The 5- and 10-year breast cancer specific survival rates were 84% and 78.6% for $pT_0T_1T_2$ versus 60.6% and 48.2% for pT_3T_4 ($p = 0.0002$) (Fig. 2).

The 5- and 10-year breast cancer specific survival rates were 81% and 79% for pN_0 versus 68.2% and 38.5% for pN+ ($p = 0.00026$) (Fig. 3).

The 5- and 10-year breast cancer survival rates were 75.8% and 70.7% for conservative surgery versus 76.6% and 63.7% for mastectomy, respectively (Fig. 4).

Twenty-three patients developed secondary cancer of various types, including four lung cancers, three skin, three thyroid and three cervix cancers.

Lately, 67 patients (35%) died and 122 were still alive. The 67 deaths were due to: breast cancer: 43 (73%), other second cancer: 7 (12%), HD or BC treatment complications: 4 (6.8%), and intercurrent disease: 5 (8.5%). In eight cases (13%), the cause was unknown.

4. Discussion

The outstanding improvement in Hodgkin's disease survival rates was unfortunately associated to long-term occurrence of various types of secondary tumours [1–6]. Acute leukaemia (especially ANLL) was the first malignancy shown to be induced by HD therapy, generally related to drug combination containing alkylating agents [19].

NHL also occurred at various intervals, especially after combination of CT and RT for HD.

ST incidence is more delayed with often a 10–20-year latency period, and continues to increase with time observation. ST were observed after RT alone, CT alone and more particularly with CT + RT association.

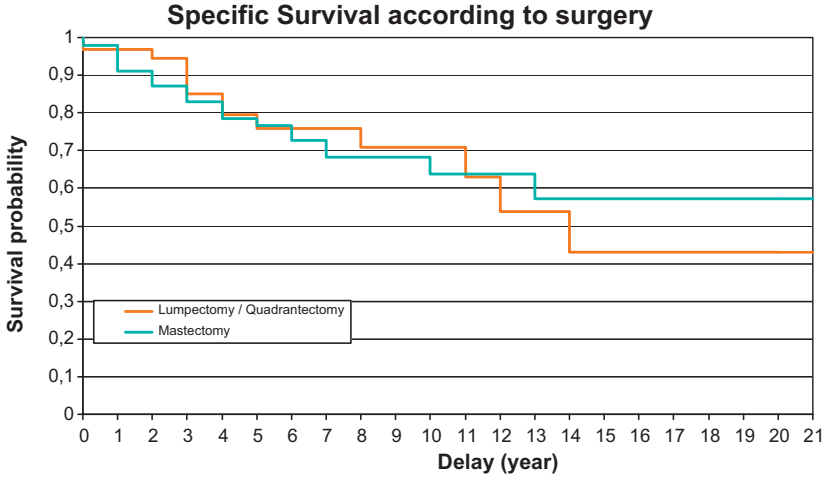

Fig. 4. Disease specific survival (DSS) rates according to surgery.

Secondary cancers represent the most important complication of HD treatments, not only in terms of morbidity, but also mortality [20]. A 10–20% 15-year cumulative incidence of ANLL, NHL and ST was reported in the majority of the series and even more with a longer follow-up. However, it is important to underline several discrepancies among these studies, with median ages at HD diagnosis varying from 11 to 43 years, wide variations in proportions among three classical HD treatments (RT/RT + CT/CT) as well as rates of HD relapses and "salvage treatments". Moreover, the follow-up range varied from 6 to 15 years. In a large German study, among 127 secondary ST occurred with a 72-month follow-up, the most frequent tumours were lung (24%), colorectal (20%) and breast (10%) [21]. Similar results were found in the largest study on 32,591 HD treated from 1935 to 1994 [1]. In a Dutch study, the RR of ST increased greatly with younger age at first HD treatment with RRs of 4.9, 6.9 and 12.7 for patients first treated at 31 to 39, 21 to 30 and under 20 years old, respectively [7]. Another very large British study including 5519 patients treated for HD confirmed that age at treatment has a major effect on risk of second malignancies [8]. Among women, breast cancer represents the most frequent ST [8–17]. After several "sporadic" reports in the 80s, many large international (often multicentric) studies confirmed a long-term high risk of BC development in children, teenagers and young women (under 25) treated for HD, especially by wide radiotherapy fields (i.e. mantle). Young age, especially "peri-pubertal" period, seems to be the most important risk factor for BC occurrence, corresponding to the highest breast radiosensitivity period.

In a Scandinavian multicentric report [6], among 670 girls treated for HD at 16-year median age (treatment modalities not specified), the cumulative risks of BC were 5% and 12% after 20 and 30 years of follow-up, respectively. In another study from Stanford [22], among 307 girls also treated for HD (RT alone: 46%, RT + CT: 51% and CT alone: 3%) at 16-year median age, the 20-year actuarial risk of BC was 9.2%. In a paediatric multicentric study [23], among 483 girls treated for HD at 11-year median age (RT alone: 23%, RT + CT: 69% and CT alone: 3%), 30 developed 42 BC at 32-year median age. Twelve out of 30 (40%) had bilateral disease. The estimated actuarial cumulative probability of BC was 17% (95% CI: 9.4–24.5) at 30 years of age. In an international multicentric study [24] conducted among 5925 young patients (<21 years) treated for HD, and including 2725 females, 52 BC were observed. In comparison with general population, the RRs were 22.9 and 11.6 among those treated from 10 to 16 and 17 to 20 years old, respectively.

A debate on the real influence of high or low RT doses, as well as large or "involved" fields used for HD cure, is still ongoing [25,26]. However, a retrospective analysis of the doses delivered to different parts of the breasts is almost impossible and the doses are often wrongly estimated due to difficulties of precise measurement [18,27]. Many parameters are variable, e.g. morphology of the patients (influenced by age treatment, height and weight, and size and shape of the breast), and irradiation modalities. The disease extent, especially the importance of mediastinal involvement, influences the field size, and consequently delivered doses to inner breast quadrants. Furthermore, especially in patients treated before the 1980s, important variations in energy used (i.e. orthovoltage, cobalt photons) and fraction doses (from 1.8 to 2.5 Gy), as well as the number of daily treated fields were observed. In two experimental dosimetric studies using a thermoluminescent dosimeter in a phantom, the measurements showed that a wide range of doses (0.6–27.4 Gy) were delivered to the breast from mantle field irradiation [27,28]. In an international case-control study [29], there were slight different BC relative risk for women treated by mediastinal RT at 20–40 Gy versus more than 40 Gy: 8.5 (95% CI: 5.4–13.2) versus 10.5 (95% CI: 6.8–16). With addition of alkylating-based CT, the risk was halved in both groups. Another Dutch case-control study including 770 women treated for HD under 41 years showed similar results [30]. In a meta-analysis of randomised trials [2], there was a significantly greater risk of secondary BC with extended-field RT (OR = 3.25, $p = 0.04$),

Table 4
Comparison between series describing BC after HD in detail.

Authors	*N*	HD age	HD treatment (%)		HD-BC delay	BC age	BC histology (%)			Death by BC (%)
			RT	RT + CT			IC	DCIS	pN + %	
Yahalom [33]	37 (45)[a]	27	73	27	15	43	82	18	31	22
Aisenberg [10]	14 (16)[a]	24	71	29	16	40	94	6	17	7[b]
Gervais-Fagnou [52]	15 (17)[a]	25	73	27	17	41	93	7	25	13
Wolden [22]	65 (71)[a]	25	58	42	18	43	87	13	27	23
Cutuli [18]	119 (133)[a]	24	62	38	15	41	90	10	54	30
El-Din [34]	28 (39)[a]	25	50	50	16	45	85	15	32	NS
Meattini [53]	39	31	54	37[c]	19.5	51	86	14	21	31
Present series	189 (214)[a]	25	28	72	18.5	42	87	13	32	23

IC, infiltrating carcinoma; DCIS, ductal carcinoma in situ.
[a] Bilateral BC (synchronous + metachronous).
[b] Short follow-up (<1 year) in seven cases.
[c] 8% treated by CT alone.

but not for all other secondary tumours. On the other hand, two studies [26,30] showed a wide increased BC risk in case of exclusive mantle radiotherapy, but with a reduced risk by irradiation of mediastinum only or associated subdiaphragmatic RT, as well as CT use. Indeed, mediastinal RT alone (without axillary field such as in classical 'mantle" field) spares approximately 50% of the breast tissues [31] (especially upper external quadrants, the most common size of BC onset). On the other hand, both CT (especially with alkylating agents) and supradiaphragmatic RT induce a high rate of permanent menopause, which is a well-known protective factor against BC, whereas the role of splenectomy or subsequent BC risk is discussed. In one report [32], splenectomy was the only variable associated with increased risk of BC, but the number of compared patients was small, with different characteristics, especially regarding age, treatment modalities and survival. Other studies did not find splenectomy as a risk factor. Those secondary BC were almost always treated by mastectomy [22,28,33,34], thinking that a conservative treatment with breast irradiation was not feasible. However, in our previous report [18], 32 out of 121 (26%) patients underwent breast conservative surgery with whole breast irradiation. The local recurrence (LR) rate was 12.5% versus 29% among 12 patients without RT after conservative surgery. No unfavourable side-effects of this treatment were observed, such as in another four reports [32,33,35,36]. In the latest report from Canada, all five patients tolerated breast RT very well, and toxicity was limited to grade-1 events [36]. The present study confirms these findings, with 56 (27%) patients who underwent whole breast irradiation after conservative surgery. The LR rate was 13.7%, according to the rates observed in young patients (<40 or <50 years) in sporadic cases in the literature [37,38].

No fibrosis or necrosis was reported. Indeed, especially after HD treatment by high dose photons (6–18 MV), and in contrast with old orthovoltage and cobalt treatments which widely increased skin and subcutaneous doses, the use of classical tangential fields (thus with different angles compared to classical antero-posterior supradiaphragmatic fields) is feasible after previous dosimetric evaluation. In our experience, many patients were treated by 1.8 Gy per fraction in order to minimize the long-term risk of fibrosis. Other teams reported some cases treated by various partial breast irradiation techniques, as well as brachytherapy or intraoperative radiotherapy with electrons [39,40]. The possibility of a new breast treatment by photons, electrons or brachytherapy was already confirmed by other studies in selected cases (small and late local recurrences) after a first radiosurgical breast conserving treatment [41,42]. On the other hand, due to a better awareness of BC risk after HD treatment both in patients and physicians, mammographic screening increased in this high-risk population. Indeed, the T_0T_1 rate was 54% (116/214) in the present study versus 44% (59/133) in the 2001 report. The T_2 rates were similar (26% and 27%), but a very important decrease in the T_3T_4 group was observed (from 18% to 6%). This global "shifting" stage explains the axillary nodal involvement fall from 54% in our previous report to 32% in our current study. Similarly, the metastasis rates decreased from 33% to 27%. Very similar data were observed in a large survey in France after full development of the national screening program [43]. Thus, an early diagnosis of these secondary BC is extremely important. Due to latency between HD treatment and BC occurrence, the mammographic screening should be started 10 years later in young women treated before 25 years [44]. Several authors recommend to add ultrasound and/or magnetic resonance imaging (MRI) to improve the screening efficiency, such as in high-risk women with BRCA 1-BRCA 2 mutations [45,46]. In a wide English screening programme, screened women had a significant reduction of BC with axillary nodal involvement (0/5 versus 7/13, $p < 0.01$), suggesting a more favourable long-term prognosis [47]. Similarly, in an experience from Toronto, 6 out of 7 clinically detected BC had axillary nodal involvement, whereas 4 out of 5 screen-detected BC were DCIS [45]. In all cases, it is important to give clear information to women and physicians on the long-term breast cancer risk, in order to perform a regular screening and facilitate diagnosis of in situ or very small invasive cancers, with a favourable long-term prognosis [48,49]. Finally, we can hope that optimal combinations of CT and involved field RT will

reduce the absolute risk of secondary BC in young patients [26,31,50,51].

5. Conclusion

Breast cancer remains the most frequent second solid cancer in teenagers and young women (10–30 years) treated for Hodgkin's disease. Median delay varies from 15 to 18 years (Table 4) [10,18,22,33,34,52,53]. The aetiology of these secondary breast cancers was complex, with several patients and treatment-related intricate factors [54].

The rate of bilaterality was approximately 15% [55]. The great majority of the tumours (85–90%) were infiltrating ductal carcinomas, with a 30% average of axillary nodal involvement.

Breast-conserving treatment including whole breast irradiation is feasible for small tumours. An accurate radiological and clinical follow-up is mandatory in these patients in order to find these secondary BC at the earliest stage [56,57].

Reviewer

Dr. Georgia Schilling, University Clinic Hamburg-Eppendorf, Oncology Center, Martinistrasse 52, D-20246 Hamburg, Germany.

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Biography

Bruno Cutuli, MD is a radiation oncologist at the Polyclinique de Courlancy in Reims, France. He formerly worked at the Curie Institute in Paris and Paul Strauss Center in Strasbourg. He is the national secretary for the French Society of Senology (Societe Française de Senologie et Pathologie Mammaire, SFSPM), and coordinator of the French Guidelines on in situ and invasive breast carcinomas. He is also the principal investigator of three recent national surveys on breast cancer in France. His research interests include breast cancer locoregional treatment, ductal and lobular in situ carcinomas, male and elderly breast cancer, radiotherapy indications and techniques and hormonal treatments. He wrote more than 150 articles and book chapters, some of which were presented in several national and international congresses. He is a member of ASTRO, ESTRO, SFRO, ESMO and EUSOMA.