BJR

https://doi.org/10.1259/bjr.20170824

Received: 26 October 2017 | Revised: 25 January 2018 | Accepted: 26 February 2018

Cite this article as:
Demoor-goldschmidt C, Supiot S, Mahé M-A, Oberlin O, Allodji R, Haddy N, et al. Clinical and histological features of second breast cancers following radiotherapy for childhood and young adult malignancy. *Br J Radiol* 2018; **91**: 20170824.

FULL PAPER

Clinical and histological features of second breast cancers following radiotherapy for childhood and young adult malignancy

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Objective: The purpose of this study was to determine the characteristics of early second breast cancer (SBC) among survivors of childhood and young adult malignancy treated with irradiation.
Methods: We conducted a multicenter retrospective study of women who presented with breast cancer aged 50 years or younger in nine French centers.
Results: 121 patients and 141 SBC were analyzed (invasive = 130; non-invasive = 11). The mean age at first cancer diagnosis was 15 years and at initial SBC diagnosis was 38 years. Bilateral disease before the age of 51 years was diagnosed in 16% of the females. The majority of SBC were invasive carcinomas (92%). Among the invasive carcinomas, 39% had a histoprognostic score of III, 3.1% overexpressed HER2 and 29% were triple negative. The proportion of triple negative phenotype SBC was higher in patients older at first cancer diagnosis [RR = 1.2, 95% CI (1.1–1.3)]. 94% of triple negative SBCs developed in breast tissue which had received ≥20 Gy.
Conclusion: We found a high proportion of aggressive SBC following thoracic radiotherapy in childhood or early adulthood.
Advances in knowledge: SBC screening is recommended by scientific societies for these child/young-adulthood cancer survivors in the same way as the one for high risk women because of constitutional mutations. Our results support these recommendations, not only because of a similar cumulative risk, but also because of the aggressive histological characteristics.

INTRODUCTION

Radiation remains an important therapy in childhood cancer: central to the treatment of some cancers, an adjunct to polychemotherapy of others, as well as the part it plays in prevention and palliative care. Nevertheless, radiation therapy is an established risk factor for a second breast cancer (SBC) among survivors of a childhood or young adult cancer.[1] Significant increases in survival rates mean that the number of people at risk of this complication is currently increasing.[2,3] Higher doses of radiation to breasts, larger field size, and younger age at exposure, increase SBC risk.[4–15] Few publications to date have investigated the histological characteristics of SBC. Most studies have been confined to survivors of Hodgkin lymphoma (HL) and reported only hormonal receptor status and not triple negative phenotype (negative for hormone receptors and HER2) status.[11,16–21] Other authors have reported that SBCs are frequently hormone receptor negative,[22,23] and that menarche status at time of radiotherapy, and amplification of the HER2 oncogene, may interact with radiation dose response,[24] though these results were not confirmed in other studies.[21,25] Studying the different subtypes of SBC may help to elucidate their carcinogenesis and open the way to tertiary prevention. This article reports a retrospective

multicenter review that aimed to characterize the histologic subtypes of SBC and to identify factors which are more frequently associated with some specific subtypes.

PATIENTS AND METHODS

Patients

Patients were recruited in nine French centers, including three centers involved in the FCCSS (French Childhood Cancer Survivor Study). The FCCSS is a cohort of 7032, 5-year survivors of a childhood cancer (*i.e.* diagnosis of cancer before the age of 18 years) treated before the year 2000: 3172 from the Euro2K cohort, the first stage of the cohort and 3860 others patients treated at Institute Gustave Roussy between 1986 and 2000. The cohort study was performed after approval from the French Data Protection Authority (CNIL) and from the ethics committee of the inserm. The centers who participated were able to deliver exhaustive data of patients.

Patients were followed up by access to medical data, self-questionnaires, and linkage with the French National Hospital Database (SNIIR-AM). Data on the primary cancer diagnosis and exposure therapy were obtained from medical records from the treating institutions. Copies of histological reports on the breast cancers were obtained.

For the six other centres, computerized records enabled the construction of an exhaustive list of patients meeting the inclusion criteria, which were: females who developed a breast cancer before the age of 51, with a past history of radiotherapy delivering at least 3 Gy to all or part of the breast during treatment for a malignancy other than breast cancer aged 30 or younger. This cut-off was chosen because females are not routinely invited to the French national breast screening program until they are 50 years old. Females who developed breast sarcoma without any epithelial component (n = 3) were excluded. Five females with a predisposition syndrome were also excluded (BRCA 1 or 2 constitutional mutation, Li Fraumeni syndrome).

Ascertainment of treatment information

Data on the primary cancer diagnosis and therapeutic exposures were obtained from medical records at the treating institutions by use of a standardized protocol. Cumulative doses of anthracyclines were determined.

Estimation of the radiation dose to the breasts during the first cancer treatment

The maximal radiation dose received by the breasts was defined as the maximal dose received by at least 2% of the volume of the breast, defined as a circle of 5 mm radius centered on the nipple for prepubescent girls, or the entire breast for pubescent girls or adult females.

(1) The radiation dose to the breast in the 54 patients from the FCCSS was estimated after reconstruction of the actual conditions of irradiation, as previously described.
(2) For the other 67 patients, two distinct methods were employed depending on the fields of the treatment plan:
    (a) For the 63 patients receiving thoracic irradiation and 3 patients receiving total body irradiation, the radiation dose to the breasts was derived from dosimetric data. Radiation planning was performed using two-dimensional plans or three-dimensional plans. The nipple was located and the dose estimated depending upon whether the nipple was in the field or its distance from the limit of the field. In the latter case, dosimetric data was obtained from a reconstruction based on a description of the beams.
    (b) For the four patients receiving abdominal irradiation, we reconstructed the dosimetry from the description of the beams, based on scans of a child of the same age and height. We have previously illustrated the risk of significant doses to the breast during abdominal irradiation, particularly in small children (less than 4 years or 1 m in height), and when an extensive field and/or high doses are employed.[5]
(3) For patients (n = 13) who had hypofractionated treatment, an equivalent dose was calculated using the linear quadratic model.[26]

If the treatment field was asymmetric, the patient was included in the study only if the affected breast was estimated to have received 3 Gy or more.

Identification and confirmation of breast cancer

Breast cancers (invasive or ductal carcinoma *in situ*) were confirmed by oncologic medical records and histological reports. Data from the contralateral breast cancers were included in the analysis if diagnosed before the age of 51 (≤50 years).

The estrogen receptor (ER), progesterone receptor (PR) and HER2 status were defined according to international recommendations: a positive result was characterized by an immunohistochemical result of ≥10% and for HER2 at 3 + or 2 + determined by amplification of the gene based on a fluorescent *in situ* hybridization procedure.[27] HER2 status was available only for breast cancers diagnosed after 1999 or 2002, depending on the center. Triple negative SBC were defined as SBC with negative hormonal receptor (ER and PR) and without any amplification of HER2.

Statistical analysis

The delay of onset was defined as the delay between the diagnosis of the primary cancer and the diagnosis of the breast cancer. Dose was analysed as an ordinal variable because of the limitations of a retrospective dose estimation, or as a binary variable (more or less than 20 Gy).

Variables associated with some studied qualitative factors were analyzed using a X^2 test or, for small samples, the Fisher test, or using a logistic regression. Linear regression was used to study possible associations between quantitative variables. All tests were considered as significant when $p \leq 0.05$. Multivariate analysis using stepwise ascendant selection was performed when several factors were significant in univariate analysis. The decision to keep a variable in the model was based on the clinical (*e.g.* age at breast cancer) or statistical significance ($p < 0.5$). To avoid correlated data, only first SBC were considered

when data of two SBC developed in the same patient were available

Missing data concerned contralateral metachronous breast cancers or older data. We did not use any imputation method but focused our analysis on recent data or on first SBC.

The statistical software used was SAS v. 9.4 TS level 1M4 and XLSTAT.

RESULTS

121 patients were included in the study, having developed a total of 141 SBC between 1977 and 2015, arising before the age of 50 years (Table 1).

First cancers were diagnosed between 1950 and 2000, at ages ranging from 0.5 to 30.6 years (mean 15.3 years), and were mostly HLs (63% of cases). The mean prescribed radiation dose was 37 Gy (range 10–45 Gy), delivered in 6 to 27 fractions over 3 days to 6 weeks. The dose received by the breasts was frequently higher than 20 Gy (69%), with a median split of about 1.8 Gy per session (1.6–3.6) (Table 1). 5 patients were treated by total body irradiation, and 16 patients (11 nephroblastomas, 2 HL, 1 NHL, 1 neuroblastoma, and 1 splenic mesenchymoma) received abdominal irradiation. 79% of the patients also received chemotherapy (52% with an anthracycline).

SBC developed at a mean age of 38 years [standard deviation (SD): 6 years], 16% before 31 years, after a mean delay of onset of 22 years (SD: 8 years).

20 females presented with bilateral disease before the age of 50 years (16%), 11 synchronously, and 9 metachronously, with a median of 6.0 (3.3–7.9) years between the diagnoses of metachronous bilateral disease. Upper outer quadrant disease predominated (36%) and 9.2% were multifocal (Table 2). Of the 141 SBC, 11 (7.8%) were *in situ* ductal carcinomas with a mean size of 20 mm (range: 2–55 mm), 4 having occurred in contralateral breast disease, (2 synchronous and 2 metachronous), at a mean age of 37 years (range: 28–44). Almost all SBCs (130, 92%) were invasive carcinomas, of which 93% ($n = 121$) were invasive ductal carcinomas (two with mucinous features), 2.3% ($n = 3$) invasive lobular carcinomas, 3.1% ($n = 4$) having both components and 1.5% ($n = 2$) medullary carcinomas. Regarding *in situ* or invasive status, there was no difference between the two groups in terms of age at first cancer diagnosis ($p = 0.4$), nor radiation dose to the breast during childhood cancer radiotherapy ($p = 0.7$).

Among the 114 primitive SBC, 20 (17.5%) were Stage $>T_3$, 32.1% had positive nodes, and 3/121 (2.5%) patients had metastasis at diagnosis. Among the 62 T_1 SBC, 28 (45.2%) were T_1a or T_1b. The invasion of the nodes depends on the size of the tumor {patients with larger cancers were more frequently node-positive: node-positive disease was, respectively, 2.4 [95% CI (0.9–6.5)], 15.6 [95% CI (3.6–66.5)] and 86.1 [95% CI (3.7–1985)] times more frequent in T_2, T_3, and T_4 patients, compared with T_1 patients} and not on the dose received by the breast during first cancer treatment.

Table 1. Patient characteristics at onset of the childhood or young adulthood cancer ($n = 121$ patients)

Characteristics	Patients n (%)
Year of the diagnosis of the first cancer	
≤1980	62 (51.2)
1981–1990	48 (29.7)
1991–1995	11 (9.1)
Age at the diagnosis of the first cancer	
<1 year	2 (1.7)
[1–5] years	15 (12.4)
[5–10] years	9 (7.4)
[10–15] years	33 (27.3)
[15–20] years	32 (26.4)
≥20 years	30 (24.8)
First cancer	
Hodgkin lymphoma	76 (62.8)
Nephroblastoma	17 (14.0)
Non-Hodgkin lymphoma	7 (5.8)
Neuroblastoma	3 (2.5)
Sarcoma	8 (6.6)
Acute leukemia, lymphoblastic lymphoma	4 (3.3)
Thyroid/oral and neck carcinoma	2 (1.7)
Medulloblastoma	1 (0.8)
Other	3 (2.5)
Chemotherapy	
No	20 (16.5)
Yes	96 (79.3)
ND	5 (4.1)
Surgery	
No	83 (68.6)
Yes	38 (31.4)
Pubertal stage at radiotherapy	
Pre-puberty	26 (21.5)
Puberty	20 (16.5)
Post-puberty	75 (62.0)
Pregnancy in the 6 months before or after the radiotherapy	3 (2.5)
Radiotherapy	
Field	
Supradiaphragmatic (mediastinal, pulmonary, +-- axillary area)	99 (81.8)
Total body irradiation	5 (4.1)
Abdominal	16 (13.2)

(Continued)

Table 1. (Continued)

Characteristics	Patients n (%)
Craniospinal	1 (0.8)
Maximal estimated dose on the breast (Gy) where SBC was diagnosed	
<10	17 (14.0)
[10–20]	19 (15.7)
≥20	85 (70.2)

Gy, Gray; ND, No data; SBC, second breast cancer.

39% of breast carcinomas had a histoprognostic score of III and concerned often triple negative SBC [79% SBC had a histoprognostic score of III, ($p < 0.05$)]. When comparing different variables related to the first cancer there was no difference between high histoprognostic score and the others (Table 2).

Hormonal status was assessed in 102/130 (78.5%) of invasive SBC, 70% of which expressed ER (ER+), and 64% expressed PR (PR+). HER2 status was determined for 65 SBC (44 after Hodgkin's lymphoma, 7 after nephroblastoma, 5 after acute leukemia or lymphoblastic lymphoma, 3 after non-Hodgkin's lymphoma, 3 after sarcoma, 3 after other types of cancer), of which only 3% overexpressed HER2, and 29% were triple negative. When adjusting on age at SBC, SBC were more frequently triple negative if developed among older patients at first cancer, after high dose received to the breast (≥20 Gy), and in females who were treated with chemotherapy without anthracycline (Table 3). 94% of the triple negative SBC developed in tissue which had previously received at least 20 Gy. In a multivariate analysis, these differences did not remaine significant. As HER2 status was often unknown, comparisons were performed between different sorts of SBC characterized by the status of hormone receptors, with unchanged results (Table 3).

An associated *in situ* component was present in 55% of invasive SBCs. Lymphovascular invasion was present in 30%.

Having a familial history of breast/ovarian cancer, a past history of a previous secondary cancers, having received chemotherapy, and age at diagnosis of SBC, did not differ according to the characteristics of SBC.

DISCUSSION

To our knowledge, this study is the first to characterize histologic subtypes and hormonal receptor status of radiation therapy-induced SBC in a group of childhood or young adulthood cancer survivors, not limited to HL survivors. Our principal finding is that invasive SBC developing in previously irradiated breast tissue are frequently (29%) triple negative (*i.e.* estrogen and progesterone negative, HER2 negative) and very rarely HER2 positive. These results are concordant with another study of 51 SBC in HL survivors, in whom 39% were found to be triple negative.[28]

In our series, all the triple negative phenotype breast cancers developed in patients treated for HL, presenting at a mean age of 20 years (6–29 years), treated with doses greater than 20 Gy to the mediastinum (except one patient) and whose treatment rarely included anthracyclines (4/17); but for the three cases of HER + SBC, the characteristics of the first cancer and its treatment are similar to the cases of triple negative SBC. To compensate the missing data of HER (which was not studied before 2000–2002), we also compared different variables analysis in different SBC characterized by their hormonal receptor status.

Aggressive histoprognostic status and triple negative status were significantly associated. These characteristics were not associated with the tumor, node, metastasis stage. As in the general population, node-status depended on the size of the tumor. Our findings are consistent with other published series suggesting that SBC frequently have aggressive characteristics.[22,24,28–31]

Among triple negative phenotype SBC, we found a higher age at the first cancer, which accords with Castiglioni et al case–control study, which reported a rate of 52% of triple negative tumors if radiation therapy had been given 4 years or more after the menarche, vs 6% if given before ($p < 0.0001$).[24] Controversially, Horst et al found similar rates of triple negative tumors in patients irradiated before (38%) and after (41%) the age of 30, but did not specifically analyze the child and young adult survivors known to be at higher risk of SBC.[28]

Breast cancer presenting at young age (frequently defined as under the age of 35 or 40) is a well-known risk factor for aggressive disease; but our study population had a higher percentage of triple negative cancers (29.2%), even when compared with reported breast cancer series in non-irradiated females aged 50 years or less at diagnosis (between 13.4 and 26.4%).[32–35] When Horst et al compared invasive SBC subtypes in HL survivors with an age-matched cohort of sporadic breast cancer patients, they also found that SBC were more likely to be triple negative (39 *vs* 14%, $p = 0.0003$). In another study of 2645 female, 5-year HL survivors diagnosed before the age of 35 in whom 166 SBC were diagnosed, Dores et al compared SBC with sporadic breast cancer in the general population and calculated standardized incidence ratios. They found that after radiation treatment for HL, the risk of negative HR status increased more than ninefold [Standardized Incidence Ratio (SIR) 9.31] and nearly fivefold for positive HR cancers (SIR 4.96). The SIR of triple negative cancers increased over time, almost doubling after 15 years (RR 1.99, SD 1.30–3.02).[23] In age- and time-adjusted multivariate analyses, the risk of triple negative SBC was still significant (RR of hormonal receptor negative SBC was 66% higher than hormonal receptor positive SBC, $p = 0.008$). In the childhood cancer survivor study, whose main study outcome was the relationship between hormone exposure and breast cancer risk:[36] among 195 females with SBC, 112 were diagnosed before the age of 40 years, 102/126 were estrogen receptor positive (83 of these were also progesterone receptor positive), 24/126 were estrogen receptor negative (19.0%) (missing data for 69 SBC). The authors analyzed different variables related to hormones in SBC with ER + adjusted for chest radiation field and dose, age at

Table 2. Characteristics of the breast cancers

	Median (range) [SD]	
Interval between the first cancer and the first SBC	21.0 (3.0–48.0) [8.2]	
Age at first SBC	38.0 (25.0–50.5) [6.2]	
Year of breast cancer diagnosis	2003 (1977–2014)	
	Number (percentage)	**Association with triple negative status p-value**
Bilateral disease, n (%)	20 (16.5)	
Synchroneous, n (%)	11 (55.0)	
Métachroneous, n (%)	9 (45.0)	
Histological feature		
In situ ductal carcinoma	11 (7.8)	
Invasive ductal carcinoma component	125 (88.7)	
Invasive lobular carcinoma component	7 (5.0)	
Medullary carcinoma	2 (1.4)	
Invasive cancers (n = 130)		
Size (n = 120)		0.97
T_1	67 (55.8)	
T_2	35 (29.2)	
T_3	11 (9.2)	
T_4	7 (5.8)	
Involved notes (n = 114)		0.89
Yes	37. (32.5)	
No	77 (67.5)	
SBR grade (n = 106)		0.03
I	25 (23.6)	
II	40 (37.7)	
III	41 (38.7)	0.0081 (III *vs* I, II)
Hormonal receptor (n = 102)		
ER + PR+	65 (63.7)	
ER − PR−	30 (29.4)	
ER + PR−	7 (6.9)	
HER2 status (n = 65)		
HER2+	2 (3.1)	
HER2−	63 (96.9)	
Triple negative (n = 65)		
Yes	19 (29.2)	
No	46 (70.8)	
Emboli (n = 67)		0.32
Yes	20 (29.9)	
No	47 (70.1)	
In situ component associated (n = 97)		
Yes	54 (55.7)	
No	43 (44.3)	

ER, estrogen receptor; PR, progesterone receptor; SBC, second breast cancer; SBR, Scarff-Bloom-Richardson; SD, standard deviation.

Table 3. Univariate and multivariate analysis—Comparison of the distributions of different variables among second breast cancer subtypes

	Triple negative phenotype (29.2% = 19/65)				Negative hormonal receptors (29.4% = 30/102)			
	Univariate		Multivariate		Univariate		Multivariate	
Factor	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age at the first cancer (per year)	1.16 (1.05–1.29)	0.0036	1.10 (0.95–1.27)	0.22	1.09 (1.02–1.16)	0.01	1.10 (0.99–1.22)	0.06
Estimated radiation dose received by the breasts (maximal dose ≥20 Gy)	11.47 (1.55–515.41)	0.007	2.26 (0.20–25.19)	0.51	5.48 (1.52–19.74)	0.009	2.82 (0.47–16.80)	0.25
Field including the pelvis	1.16 (0.40–3.40)	0.78			0.97 (0.77–1.23)	0.81		
Chemotherapy	0.43 (0.09–2.18)	0.31			1.01 (0.29–3.52)	0.99		
Anthracycline	0.20 (0.06–0.73)	0.015	0.30 (0.07–1.21)	0.09	0.38 (0.15–1.00)	0.05	0.39 (0.13–1.15)	0.09
Age at breast cancer	1.03 (0.94–1.13)	0.49	1.02 (0.88–1.19)	0.80	0.96 (0.90–1.04)	0.31	0.91 (0.81–1.02)	0.11
Year of diagnosis for breast cancer	1.00 (1.00–1.00)	0.17	1.00 (1.00–1.00)	0.27	1.00 (1.00–1.00)	0.23	1.00 (1.00–1.00)	0.43

CI, confidence interval; OR, Odds Ratio.

primary childhood cancer diagnosis, and exposure to anthracyclines. They found that the proportion of females who received more than 14000 mg m^{-2} of cyclophosphamide was significantly higher in the group of SBC without ER+ and that in that group the proportion of females who had a field of radiation therapy that included ovaries was higher.

The other general characteristics of the SBC in our study are consistent with past reports. Firstly, we found a high risk of bilateral disease (16%).[16,19,31,37–40] This may change in the future following the recent recommendations to treat HL with asymmetric radiation fields.[41–43] Secondly, the SBCs of our cohort frequently occurred in the external breast quadrants, as in previous studies among cancer survivors and as in the general population, and were frequently invasive ductal carcinoma.[11,22]

Our study inclusion criterion for a minimum dose of 3 Gy evidently makes it impossible to compare the effects of very low dose radiation, or none, with high radiation dose. In order to focus on radiotherapy-induced SBC, we excluded patients with a known predisposition syndrome, who had received less than 3 Gy to the breasts, or who were older than 50 at the time of SBC.

Fundamental studies are ongoing to identify specific profiles. SBC after irradiation has been correlated with a chromosomal instability gene profile,[44] and similarities in the deletions with those found in BRCA 1/BRCA 2 germline-deficient breast cancers have also been observed[45] consistent with our results and the phenotypes of our SBC.

In conclusion, our study provides a broad overview of the pathological features of the SBC occurring after childhood cancer treated by radiotherapy. More epidemiological and fundamental research is needed to elucidate the mechanisms of carcinogenesis of SBC, and to find strategies for prevention and appropriate treatments. Our findings suggest that radiation may contribute to the development of SBC with more adverse prognostic features.

ACKNOWLEDGEMENTS

We thank the Foundation ARC and the ANR (National Research Agency) who have funded this research.

FUNDING

In accordance with French regulations, the protocol of the study was approved by a regional ethics committee and by the Commission Nationale de l'Informatique et des Libertés (the French data protection agency). Foundation ARC, ANR.

ETHICS

In accordance with French regulations, the protocol of the study was approved by a regional ethics committee and by the Commission Nationale de l'Informatique et des Libertés (the French data protection agency).

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