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Original Paper

Breast Cancer in Patients Treated for Hodgkin's Disease: Clinical and Pathological Analysis of 76 Cases in 63 Patients

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In a retrospective multicentric analysis, 63 women treated between 1941 to 1988 for Hodgkin's disease (HD) subsequently developed 76 breast cancers (BC). The median age at diagnosis of HD was 26 years (range 7–67), and 22 women (35%) were 20 years old or less. Exclusive radiotherapy (RT) was used in 36 women (57%) and combined modalities with chemotherapy (CT) in 25 (39%). Breast cancer occurred after a median interval of 16 years (range 2–40) and the median age at diagnosis of the first BC was 42 years (range 25–73). TNM classification (UICC, 1978) showed 10 T0 (non-palpable lesions) (13%), 20 T1 (26%), 22 T2 (29%), 8 T3 (11%), 7 T4 (9%) and 9 Tx (12%), giving altogether a total of 76 tumours, including, respectively, 5 and 8 bilateral synchronous and metachronous lesions. Among the 68 tumours initially discovered, 53 ductal infiltrating, one lobular infiltrating and two medullary carcinomas were found. Moreover, two fibrosarcomas and 10 ductal carcinoma *in situ* (DCIS) were also found. Among 50 axillary dissections for invasive carcinomas, histological involvement was found in 31 cases (62%). 45 tumours were treated by mastectomy, without ($n = 35$) or with ($n = 10$) RT. 27 tumours had lumpectomy, without ($n = 7$) or with RT ($n = 20$). 2 others received RT only, and one only CT. 7 patients (11%) developed isolated local recurrence. 20 patients (32%) developed metastases and all died; 38 are in complete remission, whereas 5 died of intercurrent disease. The 5-year disease-specific survival rate by the Kaplan–Meier method was 61%. The 5-year disease-specific survival rate for pN0, pN1–3 and pN $\geq$ 3 groups were 91%, 66% and 0%, respectively ($P < 0.0001$) and 100%, 88%, 64% and 23% for the T0, T1, T2 and T3T4 groups, respectively. These secondary BCs seem to be of two types: a large number of aggressive tumours with a very unfavourable prognosis (especially in the case of pN > 3 and/or T3T4); and many tumours with a 'slow development' such as DCIS and microinvasive lesions, especially in patients treated exclusively by RT. Moreover, a very unusual rate of bilateral tumours (21%) was observed. These secondary BC could be 'in field', in 'border of field' or 'out of field'. However, a complete analysis of doses delivered by supradiaphragmatic irradiation was often very difficult, due to large variations in several parameters. We conclude that young women and girls treated for HD should be carefully monitored by clinical examination, mammography and ultrasonography. © **1997 Elsevier Science Ltd.**

Key words: Hodgkin's disease, treatment, radiation therapy, breast cancer, second malignancies
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INTRODUCTION

HODGKIN'S DISEASE (HD) is one of the malignancies in which most progress has been made in the last 30 years [1–4]. However, long-term side-effects have been observed, second primary cancer occurrence being the most important [5–8].

A connection with the treatments [9], mainly chemotherapy (CT) and radiotherapy (RT), has been documented, but genetic factors and disease-associated immunodepression may also be involved. Several reports have indicated an increased risk of secondary acute non-lymphocytic leukaemia (ANLL), non-Hodgkin's lymphoma (NHL) and solid tumours (ST) among Hodgkin's disease patients. Six recent studies [10–15] have shown that women cured of HD present an increased risk of breast cancer in long-term follow-up, especially after 15 years. The risk is very high especially in girls treated before 16 years, and persists for 30 years [10, 13–15].

A retrospective review of all women who developed breast cancer after HD in 11 French Comprehensive Regional Cancer Centres was undertaken, analysing specifically the clinicopathological characteristics of these breast cancers, the feasibility of conservative treatments in some cases, the outcome and guidelines for early detection and/or prevention.

PATIENTS AND METHODS

In a retrospective analysis in 11 centres, 63 women treated between 1941 and 1988 for HD who subsequently developed a total of 76 breast cancers were found. 15 patients (24%) had been treated for HD elsewhere and had been referred to one of the 11 centres only after breast cancer diagnosis. This fact together with the absence of complete computer registration data before 1974 makes it impossible to evaluate the epidemiological risk factors and 'real incidence' of breast cancer after HD.

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

Treatment for Hodgkin's disease

The median age at diagnosis of HD was 26 years (range 7–67 years); 22 women (35%) were 20 years old or less, three of whom were young girls (7, 8 and 9 years old, respectively). The stages of Hodgkin's disease were stage I, 11 (17%); stage II, 37 (59%); stage III, 8 (13%); stage IV, 4 (6%), and not specified in 3 (5%) cases.

The histological subtypes were lymphocyte predominance, 4; nodular sclerosis, 22; mixed cellularity, 15; lymphocyte depletion, 3; and not specified, 19.

36 women (57%) had received RT only (supradiaphagmatic alone or with subdiaphragmatic complementary irradiation) and 25 had received previous CT. The delivered doses ranged from 30 to 40 Gy, by various types of energy; the complete mantle was treated in 52 cases, 'involved fields' in 4 cases and in 7 cases a precise description of the used field was unavailable. 16 patients (25%) had splenectomy.

Only one woman, 67 years old, with a stage IV HD, was cured exclusively by six cycles of alternating CT (MOPP/ABVD) and developed left outer breast cancer 5 years later (pT2N1). She died 20 months later of metastases. Another woman, 47 years old, with stage IIIAa HD, was cured by six cycles of MOPP (plus Velbe during 15 months) and subdiaphragmatic RT only. She also developed left outer breast cancer after 9 years (pT2N1) and she is alive 9 years later after radiosurgical conservative treatment. Thus, two women did not receive supradiaphragmatic irradiation. 13 women (21%) had a subsequent relapse after various time intervals, and were treated by CT alone ($n = 6$) or by CT and RT ($n = 7$).

RESULTS

Breast cancer: clinical characteristics

The median interval after treatment of HD was 16 years (range 2–40 years) and the median age at diagnosis of the first breast cancer was 42 years (range 25–73 years). 8 women (13%) were 30 years old or younger at the diagnosis of breast cancer.

Only three women had a family history of a first-degree relative with breast cancer. The 76 breast cancers (5 and 8 patients had respectively bilateral synchronous and metachronous breast cancer) were classified in accordance with TNM (UICC, 1978): T0 (non-palpable lesions), 10 (13%); T1, 20 (26%); T2, 22 (29%); T3, 8 (11%); T4, 7 (9%); Tx 9 (12%). In five cases, inflammatory signs were present. One patient had metastases.

Breast cancer: pathological analysis

Table 1 shows the histological characteristics of the 68 unilateral or bilateral synchronous breast cancers. Ductal infiltrating carcinoma (DIC) represented 78% of the cases, but pure ductal carcinoma *in situ* (DCIS) was present in 10 cases (15%). Only one lobular carcinoma was found. Moreover, two medullary carcinoma and two high-grade fibrosarcoma (one phyllode) were noted, which developed 14 and 18 years after exclusive RT for HD. Both patients had a subsequent contralateral breast cancer, respectively, 2 and 6 years later. The 5 patients with bilateral synchronous breast cancer had DIC (SBR III, pN+) in each breast in one case; DIC (SBR II pN+ each) and contralateral DCIS in three cases; and bilateral DCIS (infraclinical) in the last case. Among the infiltrating carcinomas, the axillary involvement rate was 62%, with more than three involved nodes in 39% of cases.

Breast cancer: treatment and outcome

45 tumours were treated by mastectomy, without ($n = 35$) or with RT ($n = 10$), whereas 27 tumours were treated by

Table 1. *Histological breast cancer characteristics of* 68 *unilateral or bilateral synchronous breast cancers*

	n (%)
Subtype	
DIC	53 (78%)
SBR I	6
SBR II	18
SBR III	16
N.S.	13
LIC	1 (1%)
DCIS	10 (15%)
Medullary carcinoma	2 (3%)
Fibrosarcoma	2 (3%)
Axillary involvement*	31/50 (62%)

(pN1:7, pN2–3:12, pN > 3:12)

*Only for infiltrating lesions.

DIC, ductal infiltrating carcinoma; DCIS, ductal carcinoma *in situ*; LIC, lobular infiltrating carcinoma; SBR, Scarff, Bloom, Richardson grading.

lumpectomy, without ($n = 7$) or with RT ($n = 20$). Two others were treated exclusively by radiotherapy. One patient received only chemotherapy, and in one case, the local treatment was not clearly detailed. 32 patients received adjuvant chemotherapy and 15 tamoxifen. 11 patients (17%) developed local recurrence but only 7 without associated metastases (11%). The crude rates of local recurrence risk were, respectively, 6% and 10% after mastectomy without and with RT; and 17% and 15% after lumpectomy without and with RT. 8 other patients developed a contralateral metachronous breast cancer (one lobular infiltrating carcinoma (LIC), three DCIS and four DIC) at various intervals (from 5 to 132 months) after surgery for opposite breast cancer. Altogether, 13 out of 63 patients (21%) developed bilateral breast cancer. 4 patients developed a third primary neoplasm.

20 patients (32%) developed metastases, and all of them died. 38 patients were in complete remission. 5 died of intercurrent disease. With a median follow-up of 40 months (range 10–192) for surviving patients, median survival was not yet reached at the time of analysis. The 5-year disease-specific survival rate was 61% (95% CI = 47–75%) (Figure 1). As reported for primary breast cancer, histological axillary lymph node status (pN) and T stage are of prognostic significance. Five-year disease-specific survival rates were 91% and 66% for pN0 and pN1–3 respectively, compared with 0% for pN > 3 (median survival: 19 months) ($P < 0.0001$; Figure 2). A similar unfavourable outcome was observed for T3 and T4 tumours with a 5-year disease-specific survival rate of 23% compared with 64% for T2, 88% for T1 and 100% for T0 non-palpable tumours ($P = 0.001$; Figure 3).

DISCUSSION

The great improvement in survival rates after treatment for HD enabled the discovery in 'long-term survivors' of several complications related in part to treatment modalities. Of these, secondary cancers are the most serious [2, 5–8, 12, 16, 34, 36–38].

ANLL was the first malignancy shown to be induced by HD therapy. NHL also occurred at various intervals especially after CT and RT for HD. The incidence of solid tumours was more spread out in time: the risk continued to increase after 10 and 20 years [12, 15, 16]. Solid tumours were observed after RT alone, CT alone and especially after combined modality therapy.

Until now, only a few sporadic cases of breast cancer after HD have been reported [18–23]. Three earlier large multicentric studies [2, 16, 24] reported, respectively, 62, 39 and 44 breast cancers (representing, respectively, 9%, 6.3% and 7% of all secondary cancers), but without details about clinical staging, histological features, treatment and outcome. Very recently, two international studies and one monocentric retrospective review have brought to light a particularly high risk of breast cancer after the treatment of HD in young girls and children. In a Scandinavian report [14], among 670 patients treated for HD before the age of 20 years (median age: 16 years), the actuarial risks of breast cancer were 5.1% and 12% after, respectively, 20 and 30 years of follow-up. In the second and most recent international report [13], among 483 children treated before the age of 16 years (median age: 11 years), the cumulative risk of breast cancer rose to 35% at 40 years. A very similar long-term rate of breast cancer was

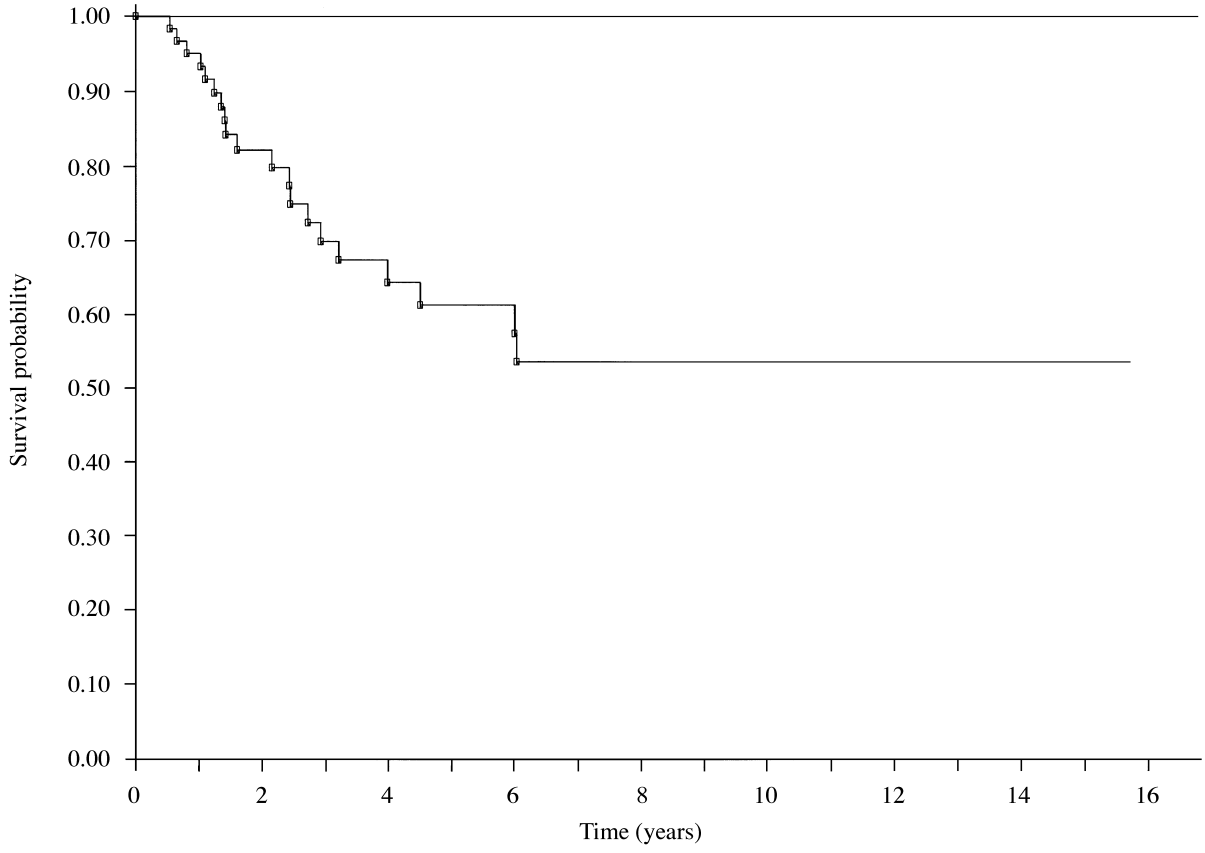

Figure 1. Disease-specific survival of breast cancer treated after Hodgkin's disease.

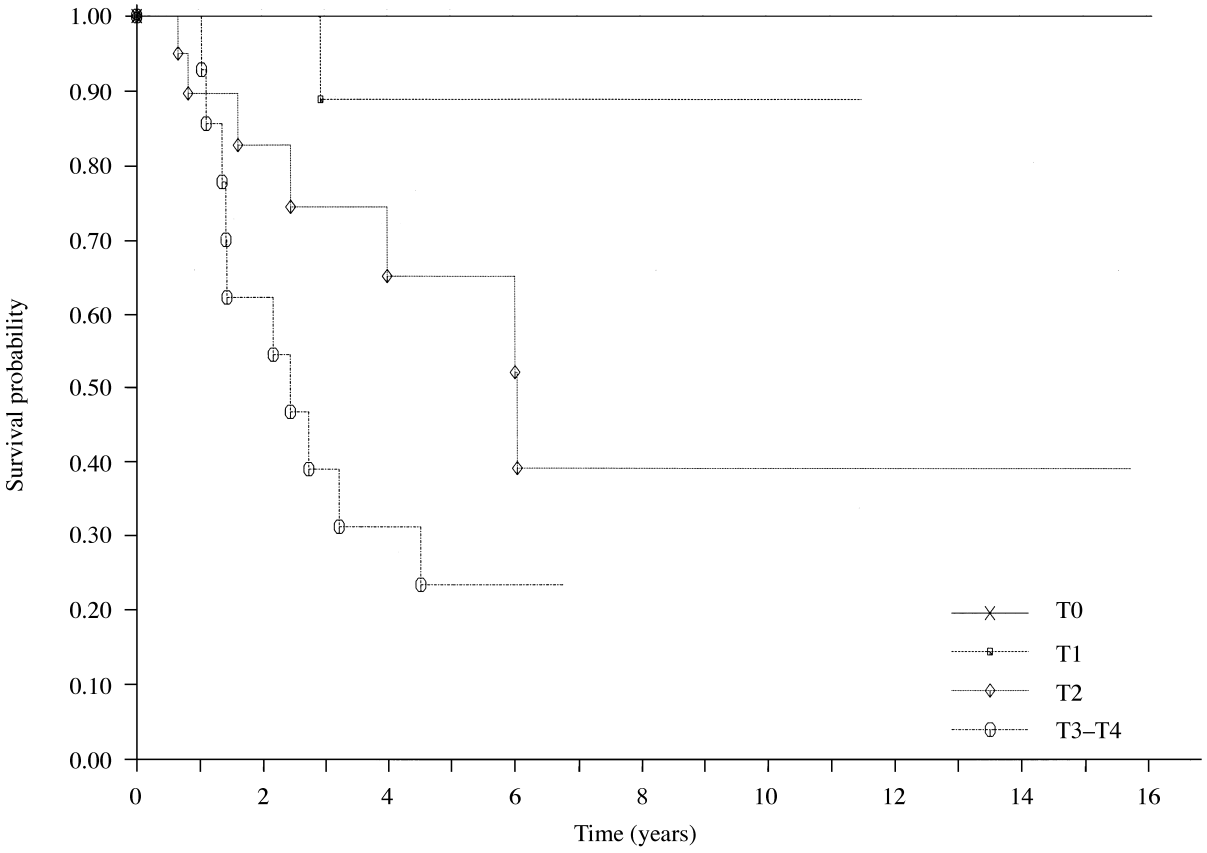

Figure 2. Disease-specific survival according to T stage.

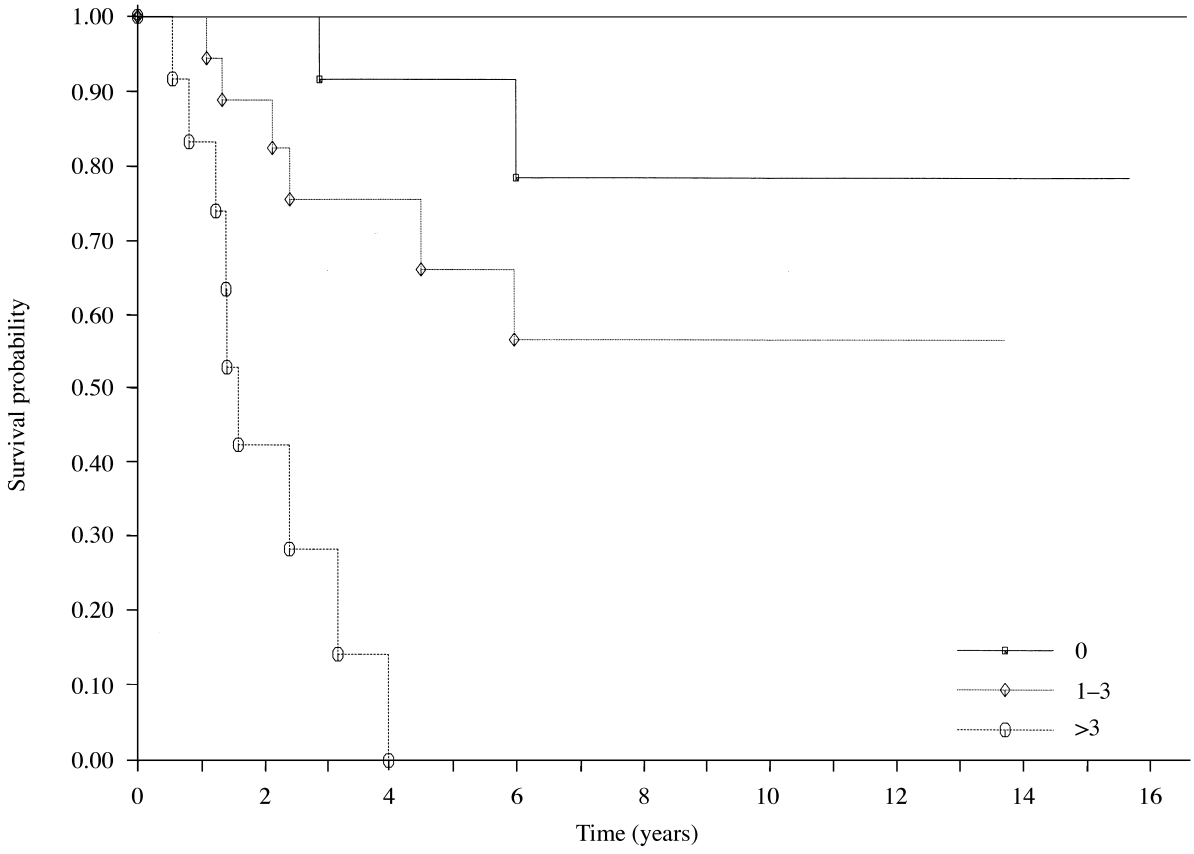

Figure 3. Disease-specific survival according to pN status.

found among 33 women younger than 20 years at the time of irradiation in the Boston experience [15]. However, only in the last one and in two other studies [10, 11] were clear details concerning the clinical and histological characteristics of these secondary breast cancers presented. Table 2 compares these data to our series.

The most striking result is the median interval between HD and breast cancer diagnosis: approximately 15 years for all series. Concerning the histological features, we noted in our series a very high rate of axillary node involvement (62% versus 31% in Yahalom's series), and two cases of breast sarcoma, never reported before. The globally high proportions of DCIS (16 and 17.7%) were also very similar. The rate of bilateral cancer (synchronous or metachronous) was also extremely high: 21% in our series, 21.5% in Yahalom's series [11], and 29.4% in the paediatric series reported by Bathia and colleagues [13]. In standard series of breast cancer, this rate varies from 0.3% to 3% and from 7% to 12%, respectively, for synchronous and metachronous tumours [25–27].

Many epidemiological studies have confirmed an increased long-term risk of breast cancer after exposure of the breast to low doses of ionising radiation [28–30]. All these studies indicate that the younger the age at which the person is exposed to radiation, the higher the risk of 'secondary' radiation-induced breast cancer. Sensitivity to RT-induced cancer is strongest during infancy and childhood. For the breast, puberty is probably the most radiosensitive period [14, 15].

The Stanford study [10] clearly showed the strong correlation between the risk of breast cancer and the age of HD treatment. For the girls who received irradiation before 15 years of age, the relative risk (RR) of subsequent breast cancer was 136, whereas for those treated between the ages of 15 to 24 and over 24, the RR were, respectively, 24 and 7. However, no increase in risk was found for patients irradiated at or after 30 years of age. Similar results were found in three other studies [13–15]. In our series, 33 out of 63 patients (52%) were treated for HD before the age of 30 years. In the New York series [11] this rate was very similar with 25 out of 37 women (68%) under 30 years, but the prognosis seemed less unfavourable.

Breast cancer risk analysis for the population of women whose breasts were exposed to radiation showed a linear dependency with the radiation dose up to 10 Gy. In fact, multiple data suggest that carcinogenic risk is more important at a low or intermediate level of radiation than at the higher doses which kill all cells [28–30]. A retrospective analysis of the doses delivered to breasts is almost impossible. Many parameters are variable, e.g. the morphology of the patients (influenced by age at treatment, height and weight, size and shape of the breasts) and irradiation techniques [31, 32]. In fact, a large number of gradient doses exist due to different energies [8], different shapes in complex fields with use of complete mantle or subtotal mantle (e.g. without inclusion of axillary areas which notably reduce the irradiation of upper out breast quadrants), and differences concerning the lung protection blocks [31, 32]. All these factors explained clearly that a 'predictive model' concerning the real carcinogenetic risk for the breast after treatment for HD by irradiation was impossible to define. Moreover, the exact 'additive effect' due to chemotherapy (especially with alkylating agents), genetic predispositions (genes *BRCA 1*, *BRCA 2* or Ataxia–telangectasia) and chronic immunodepression due to HD or related to treatment is uncertain.

The treatment of these 'secondary' breast cancers needs imperatively a multidisciplinary approach [33]. An analysis of the previous technical parameters of the supradiaphragmatic irradiation is mandatory (especially doses and field shapes) according to the location of the second breast cancer. These breast tumours can be 'in field', in 'border of field' or clearly 'out of field'. In the case of a limited and unifocal lesion, conservative radiosurgical treatment is sometimes feasible [33]. Among the 20 tumours treated by radiosurgical conservative association, no particular side-effect was observed. The whole breast could be treated by conventional tangential fields, but preferably by daily fraction of 1.8–2 Gy. The total dose could be limited to 45 Gy, with a boost given by electrons or brachytherapy at 10–15 Gy. The chest wall could also be irradiated, but the nodal irradiation is much more difficult.

In spite of long-term side-effects, it is necessary to remember that radiotherapy and chemotherapy allow us to save a very large number of patients who previously had no hope of survival. At the moment, attention should be focused especially on the optimal treatment of childhood Hodgkin's disease, because this group clearly runs a high risk of developing secondary cancers, such as breast cancer in girls and adolescents [10, 15, 34]. We agree with Donaldson's comments [35, 36] and think that an optimal combination of therapy, using initial chemotherapy without alkylating agents and 'involved' field at moderate doses (20–25 Gy with daily fraction of 1.8 Gy and optimal dose distribution with megavoltage photons), could obtain a definitive reduction of leukaemia and solid secondary tumours. Finally, our study seemed to define two types of secondary breast tumours: a large number of very aggressive tumours, with important axillary involvement and other unfavourable histological characteristics; and many tumours with a long-term 'latent period', mainly of the DCIS or microinvasive type. These

Table 2. Literature data

Study (Ref.)	*n*	Median age (HD)	Treatment (HD)			Median delay, years HD-breast cancer	Median age, years (breast cancer)	Histology (all cases of breast cancer)				Second breast cancer		Evolution		Died of breast cancer
			CT	RT	CR + RT			IC	DCIS	Sa	pN+	Syn	Met	LR	M	
Hancock [10]	25	28	1	12	12	15	40	25	—	—	NS	—	—	NS	10	7 (28%)
Yahalom [11]	37 (45)*	27	—	27	10	15	43	37	8	—	31%	4	4	NS	9	8 (21.6%)
Aisenberg [15]	14 (16)*	24	—	10	4	16	40	15	1	—	17%	—	2	NS	1	1‡
Present series	63 (76)*	26	1	36	26†	16	42	62	12	2	62%	5	8	11	20	20 (32%)

*Bilateral synchronous or metachronous breast cancer. †One patient has subdiaphragmatic irradiation. ‡Short follow-up ($\leq$ 1 year) in 7 cases. NS, Not specified; LR, locoregional recurrence; M, metastasis; Syn, synchronous; Met, metachronous; IC, infiltrating carcinoma; DCIS, ductal carcinoma *in situ*; Sa, sarcoma.

lesions seemed to develop more frequently in women treated exclusively by radiotherapy.

Consequently, the young women treated for HD should be carefully monitored by clinical examination, mammography and ultrasonography. The optimal schedule of this follow-up is unknown, but a first senologic check up should be suggested at least in the tenth year after HD treatment, especially if other associated breast cancer risk factors are present [34].

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