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Breast cancer after childhood irradiation

Clinical and diagnosis characteristics of breast cancers in women with a history of radiotherapy in the first 30 years of life: A French multicentre cohort study

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ABSTRACT

Purpose: Irradiation (>3 Gy) to the breast or axillae before 30 years of age increases the risk of secondary breast cancer (SBC). The purpose of this article is to describe the clinical characteristics of SBC and the way of diagnosis in young women (before the age of national screening) in France who had received previous radiotherapy for a childhood or a young adulthood cancer.

Patients and methods: This retrospective, multicentre study reviewed the medical records of women with SBC before the age of the national screening who had received irradiation (≥3 Gy) on part or all of the breast before 30 years of age, for any type of tumour except BC.

Results: A total of 121 SBC were detected in 104 women with previous radiotherapy. Twenty percent of SBC were detected during regular breast screening and 16% of the women had a regular radiological follow-up.

Conclusion: Our results points out that the main proportion of childhood cancer survivors did not benefit from the recommended breast cancer screening. This result is comparable to other previously published studies in other countries. A national screening programme is necessary and should take into account the patient's age, family history, personal medical history and previous radiotherapy to reduce the number of SBC diagnosed at an advanced stage.

Breast cancer (BC) is a major complication in survivors of cancer at a young age [1,2]. The number of people at risk of secondary breast cancer (SBC) has increased due to the significant improvements in cancer survival, with cure rates of >80% for childhood cancers and Hodgkin's lymphoma (HL) [3]. However, 40%–70% of previous cancer patients present with health problems linked to their disease or to the treatments received [4–6], and 60% are at risk of developing chronic sequelae [7].

The role of irradiation in the genesis of SBC has been known for many years [8,9]. These SBC occur within or close to the irradiation zone [10–12]. The cumulative risk is considered to be 35% at 40 years of age following mediastinal irradiation (≥20 Gy) [13], compared to only 12.4% in women in the general population. This risk is similar to that in the high risk population that present with predisposing BRCA1 [14] or BRCA2 [15] germ-line mutations. It is difficult to define a threshold dose for increased risk because the risk also depends on parameters such as the size of the irradiation field, the staging and fractioning of radiotherapy, age at the time of treatment, hormonal infusions, etc. However, analytical studies have shown a significant risk of SBC even at low doses (3 Gy) [16–19].

Many studies have been carried out over the past few years on the evolution of patients who survive childhood cancer. Specialised follow-up is often organised for patients at risk of developing complications in order to detect them early and to optimise their management. To this end, breast screening is recommended for women at high risk of SBC [20,21]. A similar programme of breast screening has already been studied in women with BRCA mutations [22,23].

The present study was carried out in order to have an overview of the follow-up of the recommendations about breast screening in childhood cancer survivors in France. Its purpose is to describe the

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clinical characteristics of SBC and the way of diagnosis in young women (before the age of national screening) in France who had received previous radiotherapy for a childhood or a young adulthood cancer.

Patients and method

Selection of patients and data collection

Patients were recruited from eight French centres, who were able to do an exhaustive research in medical files and from the French patients of the Euro2K database, which is a cohort of childhood solid cancer survivor [19,24]. To be included, women should have all these inclusion criteria: a personal past history of treatment for cancer before 30 years of age, and, who had received radiotherapy at a dose of $\geq$3 Gy over all or part of the breast, and, who developed SBC at $\leq$50 years of age. This upper age limit was chosen because this is the age at which organised breast screening starts in many countries. Women were excluded if the first cancer was a breast cancer.

The following data were recovered for each patient: data regarding the initial cancer (histological diagnosis, mode of treatment including details of the irradiation administered, sequelae). For each patient with SBC, clinical data (mode of detection, radiological characteristics) and prognostic factors (TNM stage) were recorded.

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

Definition. The maximal radiation dose received on the breasts was defined as the maximal dose received by at least 2% of the volume of the breast, considered as the whole mammary gland of a pubescent girl or as an area covering 5 mm around the nipple for prepubescent girls.

Dose estimation.

1- To estimate the radiation dose received to the mammary gland during radiotherapy of patients from the Euro2k cohort, the radiation therapy was reconstructed from technical records using homemade software which was previously described [25]
2- For the other patients, 2 distinct methods were employed depending on the field of the treatment plan:

For the ones treated on the thorax and for the patients who were treated by total body irradiation, the radiation dose received by the breasts was estimated using the dosimetric data. Radiation planning was realised after 2D plans or 3Dplans. Nipple was located and estimation of the dose was realised depending if the nipple was in the field or depending of the distance with the limit of the field. For this second case, reconstructions were done if the radiation treatment used a 3D plan, using dosimetric report using description of the beams. Otherwise, an estimation was done by local physicians and radiotherapy oncologists. If a minimal 3 Gy received dose was uncertain, it was decide to not include these patients (2 cases).

To estimate the delivered dose to the mammary gland of the patient irradiated on the abdomen, we reconstituted the dosimetry using dosimetric report using description of the beams on the personal 3D scans if possible or on a scanner of a child with the same age, sex, and size.

If asymmetric field, the patient was included in the study if the breast where the cancer occurred was estimated to have received 3 Gy or more.

Two patients for whom parameters of the radiation treatment were not enough to estimate the dose received by the breasts were excluded of the study.

Ethics

In accordance with French regulations, the protocol of the study has been approved by a regional committee on ethics and by the national committee protecting the confidentiality of the data (Commission Nationale de l'Informatique et des Libertés).

Statistical analysis

The time of onset was defined as the time between the two diagnoses (first cancer and breast cancer). Descriptive statistics and comparisons (chi squared or Fisher's exact test) were used to describe the cohort using SAS version 9.2. A p-value ≤ 0.05 was considered as significant.

Results

Characteristics of the initial cancer

One hundred and four women ($\leq$50-year of age) with 121 breast tumours were included in the study (67 from the eight centres and 37 from the Euro2k cohort). Mean age at diagnosis of the initial cancer was 16.3 years (range: 0.6–30.6); this was HL in 71% of cases. The initial cancer was treated between 1950 and 1995 with a total dose of $\geq$3 Gy over at least part of the breast, in 6–27 sessions spread over 3 days to 6 weeks. The majority of patients received radiotherapy to the mediastinum at a dose of between 9 and 50 Gy, with a median fractionation of 1.8 Gy/session (1.6–3.6). Five patients received total body irradiation delivered a dose of 12 Gy as bi-fractions over 3 days. For nine patients (six nephroblastomas, two HLs and one mesenchymoma of the spleen), irradiation involved the abdomen and part of the breast, at a dose of $\geq$3 Gy.

Characteristics of secondary breast cancers

Mean age at the first SBC diagnosis was 37.3 years [range: 23.5–50.3] [Table 1]. The median year of diagnosis was 2002 (1977–2010). The mean interval between the initial cancer and the diagnosis of SBC was 20.6 years [95%CI: 13.6–27.6]. For five patients who developed SBC < 10 years after radiotherapy, mean age at the initial cancer diagnosis was 25.1 years [14.6–29.9]; four of these patients received radiotherapy of the mediastinum at 40 Gy for HL and the fifth had bilateral pulmonary radiotherapy. Seventeen women (16.3%) presented with bilateral SBC; for seven, the disease was synchronous and for ten it was metachronous, with a median time of 5.9 years [3.3–7.9] between the two. Of the 12 young girls whose field of radiotherapy was preferentially unilateral, only one presented with SBC on the opposite side (but whose breast had at least partially received 3 Gy); for the rest, SBC occurred on the side that had received the most irradiation. As for BC in the general population, SBC was mainly located in the upper outer quadrant (50%; all other locations between 4.4% and 11.1%).

The first SBC was diagnosed at the symptomatic stage in 88.3% of cases (pain, lump, discharge or skin retraction); 21.2% of the women had benefited from breast surveillance before SBC diagnosis, either clinical (4.8%) or by annual/biennial mammography (15.4%) or by biannual echography and mammography for one patient at high risk (50 Gy to the mediastinum and three family cases of BC). Only one of these screened patient was diagnosed in the interval between two biennial exams.