

Breast conserving treatment

Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first[☆]

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Abstract

Purpose: To ascertain the loco-regional recurrence (LRR) rate and its major prognostic factors in patients younger than 40 and to determine the influence of age on the features of breast cancer and its treatment in two age groups: ≤ 35 years and [36–39] years.

Methods and materials: Between 1985 and 1995, 209 premenopausal women, younger than 40, were treated for early breast cancers with primary breast conserving surgery followed by radiotherapy $\pm$ chemotherapy. Median age was 37 years with 66 patients (32%) ≤ 35 years and 143 older (68%). Median follow-up was 12 years. Tumours' characteristics were: cT1 in 75%, pN0 in 60%.

Results: LRR rate was 38% at 10 years, contralateral breast cancer rate 12%. Age was the only prognostic factor for LRR. The relative risk of LRR increased by 7% for every decreasing year of age. The annual risk of local recurrence peaked between 2 and 3 years after the initial diagnosis and returned to the level of contra-lateral breast cancer at 10 years.

The younger population had infiltrating carcinomas that were significantly more commonly ductal, less commonly lobular, and of higher grade – they received chemotherapy more often.

Conclusion: Using conventional methods we could find no explanation as to why age remained the most important prognostic factor for breast cancer LRR. Known prognostic factors such as involved surgical margins seemed erased by adequate radiotherapy doses.

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Young age is recognized by most authors as a major prognostic factor for worse local control [1–9]. Others, however, are still debating this issue [10–12]. Our purpose was to determine the prognostic factors of loco-regional control in a homogeneous population of young (<40 years), pre-menopausal women treated with breast conserving surgery for early stage breast cancers in this era of immuno-histochemical diagnosis.

We also determined the influence of age on the features of breast cancer and on its treatment in two age groups: very young (≤ 35 years) and intermediate age ([36–39]). We chose 35 years as a cut-off to compare sub-populations

according to age because it had often been used in the literature [1,7,13–17].

Finally, we compared the evolution of annual risks of local relapse, either at the site of the initial breast cancer or at a different site, with that of contra-lateral breast cancer.

Patients and methods

We report here a retrospective study of 209 pre-menopausal women, younger than 40 years old, treated at the Institut Curie between 1985 and 1995 for early breast cancers. Median age at diagnosis was 37 years (23–39) with 32% of patients (66 patients) 36 years old or younger and 68% between 36 and 39 years old (143 patients). Median follow-up was 12 years (1–20). The minimum

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follow-up of patients still alive at the time of analysis was 1 year.

Patients' characteristics were: clinical tumour stage [18] was T1 in 75% (157 patients) and T2 in 25% (52 patients). N-stage was N0 for 97% (202 patients), N1 for 3% (9 patients).

All the specimens were reviewed by the same pathologist (BSZ). Histological classification, according to the WHO criteria, was: 177 (85%) ductal, 10 (5%) lobular and 22 (11%) other types of infiltrating carcinomas. Histological grade (Ellis Elston [19]) was scored 1 in 66 patients (32%), 2 in 83 (40%), 3 in 45 (22%) and unknown in 15 (7%). The median number of mitoses per 10 high power fields [20] was 5 (0–120). Hormonal receptors (HR) were positive in 157 (75%) as they showed staining of either estradiol receptors (ER) or progesterone receptors (PR) in at least 10% of cells by immuno-histochemistry. Axillary lymph node status was negative in 60% (126 patients).

The information relative to HER2 over-expression has been studied by immuno-histochemistry. However, as it needs confirmation by FISH, it will be reported elsewhere.

Treatments

Surgery

Surgery consisted in breast conserving procedures as the first treatment in all cases. The quality of the surgical margin was stated as wide (>3 mm) in 136 patients (65%), close (≤ 3 mm) in 42 (20%), involved with ductal carcinoma in situ in 20 (10%), involved with invasive carcinoma in 9 (4%) and unknown in 2 patients (1%). Axillary lymph node dissection was performed in 83% (173 patients) of women.

Radiotherapy

Patients received post-tumorectomy radiotherapy with a median dose of 54 Gy (45–63) to the breast. A boost to the tumorectomy bed was performed for 53% (111 patients) of women with a median dose of 15 Gy (2–25). The mean total dose to the tumorectomy bed was 61 Gy (50–77). Axillary irradiation, using an extra field, was performed in 34% of patients (71 patients). Supra-clavicular irradiation was performed in 30% (63 patients) of women. Internal mammary irradiation was performed in 68% (141 patients) of women. In the case of a lymph node involvement both the internal mammary chain and the supraclavicular area were irradiated. In the absence of a lymph node involvement, the irradiation of the internal mammary chain, with or without the supra-clavicular area, was decided on for centrally located tumours with histological features of aggressiveness. The irradiation of the axilla was added when there was an important axillary involvement or in the absence of an axillary lymph node dissection. Two patients had nevertheless neither axillary lymph node dissection nor axillary irradiation.

There was no protocol to boost all young patients with negative surgical margins at that time and some of the patients reported in this series were accrued in the EORTC boost trial that randomized from 1989 to 1996 between boost and no boost [1,8,21]. In the case of positive surgical margins, a radiotherapy boost of generally 20–28 Gy was added to the whole-breast irradiation. For patients who were not participating in the EORTC randomized trial,

a boost of 10–16 Gy was added in the case of aggressive histological features (unsatisfactory margins, high histological grade, high proliferation index, absence of hormone-receptors).

The total dose to the tumorectomy bed was thus highly dependent on surgical margins with 69% of total dose ≥ 60 Gy, usually with brachytherapy, in patients with close or involved margins and 48% with large (≥ 3 mm) margins ($p = 0.0004$). The reasons for the absence of re-excision were not always specified. When they were it was because of the patient's choice not to undergo a new surgical procedure that could have been a mastectomy.

Systemic treatments

Systemic treatments were given in 30% (63 patients) of women. At the time of treatment, the protocol for pre-menopausal women consisted of anthracycline-based polychemotherapy (usually 6 cycles of 5-fluorouracil, doxorubicine, cyclophosphamide) without hormone-therapy.

Statistics

Survival rates, defined from the date of the surgery, were estimated using the Kaplan–Meier estimate – the groups were compared using the Log rank test. Overall survival was defined as death from any cause. Local relapses were defined as the occurrence of breast carcinoma in the treated breast. Loco-regional relapses were defined as either a local relapse or a recurrence in the ipsilateral lymph node bearing areas (axillary, internal mammary, supra-clavicular). Contra-lateral breast cancers could be either ductal in situ or infiltrating carcinoma. Distant disease was defined as recurrences of breast carcinoma neither in the contralateral breast nor loco-regional. Disease-free was defined as the absence of loco-regional and/or distant relapses.

Survival rates and relative risks (RR) are presented with their 95% confidence intervals (CI). Annual risks were calculated and plotted.

To compare percentages Fisher's exact test or Chi-2 was used as appropriate.

All the following factors were studied: age at diagnosis as a continuous covariant and divided in classes (≤ 35 years vs. [36–39] years), maximal diameter of the tumour either clinical (T_1 vs. T_2) or histological (pT_1 vs. pT_2), axillary lymph node involvement in either 5 classes (no axillary lymph node dissection vs. pN_0 vs. pN_1 vs. pN_2 vs. pN_3) or 3 classes (pN_0 vs. pN_x vs. pN_{1-3}), histological type of the infiltrating carcinoma (ductal vs. lobular or other), hormonal receptors (ER+ vs. ER– and PR+ vs. PR–), lympho-vascular extension, histological grade according to Ellis and Elston (either grade 1 vs. grade 2 vs. grade 3 or grade 1 vs. grade 2/3 or grade 1/2 vs. grade 3), tubular formation (either grade 1 vs. grade 2 vs. grade 3 or grade 1/2 vs. grade 3), nuclear polymorphism (grade 1 vs. grade 2 vs. grade 3), number of mitoses per 10 high power fields (either ≤ 10 vs. [11–21] vs. > 21 or ≤ 21 vs. > 21), quality of the surgical margin (either involved vs. narrow ≤ 3 mm vs. wide > 3 mm or involved/narrow vs. wide) and use of adjuvant chemotherapy. Radiotherapy criteria were also studied, i.e., the total dose to the tumorectomy bed in either 3 classes (≤ 54 Gy vs. [55–64] vs. ≥ 65 Gy) or 2 classes (< 60 Gy vs. ≥ 60 Gy).

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