Late local recurrences in a randomised trial comparing conservative treatment with total mastectomy in early breast cancer patients

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Background: A randomised trial was conducted comparing wide lumpectomy and breast irradiation with modified radical mastectomy. As the follow-up was long (mean duration 22 years), we analysed the variation in the effect of treatment over time.

Patients and methods: The trial included 179 patients with a breast cancer measuring ≤2 cm at macroscopic examination. Eighty-eight patients had breast-conserving surgery and radiotherapy, and 91 underwent mastectomy. All patients had axillary dissection. The analyses were based on Cox models with time-dependent treatment effects.

Results: The effect of treatment on death or metastasis did not vary with time. The risk of local recurrence was lower during the first 5 years for the breast-conserving surgery group as compared with the mastectomy group, but higher after 5 years (P = 10^-4 for a different treatment effect over time). Similar results were found in a database including 1847 patients with small breast tumours at diagnosis. In this analysis, late breast recurrences were also more frequent in the breast-conserving surgery group and this treatment effect was greater among younger patients (≤40 years at the time of diagnosis).

Conclusions: Late breast recurrences were more frequently observed in younger patients treated with breast-conserving treatment compared with those submitted to mastectomy. These results require confirmation in other randomised studies so that younger patients with early breast cancer can receive adequate counselling and so that a more stringent long-term follow-up policy can be adopted when breast-conserving treatment is planned.

Key words: breast-conserving surgery, early breast cancer, late local recurrence, randomised trial, total mastectomy

Introduction

During the last three decades, seven randomised trials comparing mastectomy with limited surgery and breast radiotherapy have been published [1–7]. In all trials but one [3], as well as in the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview [8], no differences were found in overall and relapse-free survival between the two treatment options. However, long-term results in breast-conserving surgery (BCS) series are cause for concern, essentially because of local control rates [6, 9–12].

We previously reported 15-year results of one of these randomised trials [5] and we report now the 22-year results focusing on the time-dependent variation in the effect of treatments on different events.

Patients and methods

Trial design

The study design has been described previously [5, 13]. Briefly, between October 1972 and September 1979, all patients <70 years old, with a unilateral breast tumour classified T1, N0–1, M0 [14] were considered eligible. They were informed of the two surgery options. Eligible patients first underwent lumpectomy for diagnosis at frozen-section examination. When the tumour measured ≤2 cm at macroscopic examination, the patient was considered definitively eligible and the operative procedure was randomly allocated: modified radical mastectomy sparing the pectoral muscles versus wide lumpectomy with a 2-cm margin of normal glandular tissue around the tumour mass.

Axillary dissection of level I nodes was carried out in all patients, followed by frozen-section examination of at least seven lymph nodes. Complete axillary dissection was done only in patients presenting at least one involved axillary lymph node.

All patients included in the BCS group received breast irradiation at a dose of 45 Gy in 18 fractions over 30 days using cobalt 60 photon beams. A boost dose of 15 Gy in six fractions was delivered to the tumour bed.
Patients with histologically proven negative axillary lymph nodes did not receive nodal irradiation. Patients with positive axillary nodes (N+) were offered random allocation to postoperative nodal irradiation versus no further treatment. When lymph node radiotherapy was carried out, a total dose of 45 Gy in 18 fractions was delivered to the axilla, and the supraclavicular and internal mammary chain areas. In total, 25 patients with N+ disease out of 58 did not receive lymph node irradiation (11 in the BCS group and 14 in the mastectomy group). Beam arrangements have been described elsewhere [13]. No patient received adjuvant chemo- or hormonal therapy. After completion of treatment, patients were seen every 4 months for the first 2 years, then every 6 months up to 5 years, and yearly afterwards, with a yearly mammogram and a clinical examination at each visit. Complementary examinations were requested in cases of clinical symptoms or signs.

The histopathological diagnosis of breast recurrences was reviewed and compared with that of the initial tumour taking into account: cytological, morphological/architectural and stromal patterns, histological grade and immunohistochemical staining (hormonal receptors, c-ErbB2, E-cadherin and CA 15-3). The majority of these parameters had to be similar for a given lesion to be declared a true recurrence.

To verify the validity of the results obtained for local recurrence and contralateral breast cancer (CBC), we also analysed 1847 patients (632 had a BCS and 1215 a total mastectomy) abstracted from the Institut Gustave-Roussy (IGR) 1954–1983 database but not included in this trial. All these patients presented with a macroscopic tumour measuring ≤2.5 cm and received the same irradiation protocol as the patients in the trial.

Statistical methods

The trial was designed as an equivalence trial to test the following null hypothesis of no equivalence, namely that the 5-year overall survival rate would be <85% in the BCS group and attain 95% in the mastectomy group. With a one-sided alpha risk of 0.10 and a power of 0.90, 165 patients were required.

Randomisation lists were generated by blocks of six patients. The resulting treatment allocations were placed in numbered and sealed envelopes, which were opened by the pathologist when the patient was definitely eligible. The randomisation result was then communicated to the surgeon.

The primary end point was death and secondary end points were total tumour events. Multivariate Cox models [15] were used for long-term analyses in two steps: (i) We first tested whether the effect of treatment was constant over time for each type of event [16]: death, local recurrence (chest wall or breast), regional (lymph node) recurrence, distant metastasis, CBC and new primary malignancies (NPMs). (ii) When treatment effects were not constant over time, the time axis was split into two periods (before/after 5 years) to quantify these effects in each period [16]. Cox analyses were stratified on nodal status and nodal irradiation, and adjusted on age group (≤40, 41–50, 51–60, >61 years).

Local recurrence and CBC rates were also analysed by treatment group in patients from the IGR database with a Cox model adjusted on age groups, axillary node involvement, histological grade [17] and tumour size.

Results

Clinical and histological findings

The trial included 179 patients: 91 in the mastectomy arm and 88 in the BCS arm. No protocol violation was observed. As previously reported [11], no differences were detected between the two treatment groups in terms of age, macroscopic tumour size, histological grade and the number of histologically proven negative axillary nodes. The follow-up period was similar for both groups: 22.7 years [standard deviation (SD) 3.5 years] versus 22.1 years (SD 3.5 years). Only four patients, who were not born in France, were lost to follow-up before 1998 in each group. The last IGR visit was between 1998 and 2001 for all other survivors. The following follow-up modalities were considered.

Variation in treatment effect with time

Table 1 details the variation in the treatment effect with time for each type of event. The treatment effect was not constant over time for local recurrence and CBC. The mean interval between randomisation and the occurrence of a local recurrence was six times longer in the BCS group than in the mastectomy group. For CBC the mean interval was twice as long as in the BCS group but there were no differences between groups in terms of other events.

Multivariate analyses for each type of event

The risks of death and metastasis were in favour of the BCS group (Table 2, Figure 1), but the differences were not significant. Similar results were observed for the risk of regional recurrence and NPM. Outcome regarding the risk of CBC was more favourable in the BCS group during the first 5 years of follow-up and in the mastectomy group after 5 years, but this difference between the follow-up periods was not significant (P = 0.25). A similar variation was observed for local recurrence, but the difference between

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Conservative treatment (n = 88)</th>
<th>Mastectomy (n = 91)</th>
<th>P value for constant treatment effecta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events</td>
<td>Mean interval, years (SD)</td>
<td>No. of events</td>
</tr>
<tr>
<td>Death</td>
<td>35</td>
<td>11.9 (6.6)</td>
<td>46</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>24</td>
<td>6.5 (4.8)</td>
<td>32</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>2</td>
<td>6.2 (2.6)</td>
<td>7</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>6</td>
<td>11.7 (9.2)</td>
<td>9</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>15</td>
<td>10.5 (5.9)</td>
<td>10</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>14</td>
<td>13.7 (7.3)</td>
<td>9</td>
</tr>
</tbody>
</table>

*a* A significant P value means that the treatment effect is not constant over time.

SD, standard deviation.

Table 1. Variation of treatment effect with time according to type of event and treatment group
the risk of local recurrences before and after 5 years was highly significant (P = 0.0001). Thus, the risks of local recurrence in the BCS group were five-fold less during the first 5 years, but 12-fold greater after 5 years. Local recurrence and CBC rates are shown in Figure 2.

**Age of patients at diagnosis and local recurrence according to treatment**

The age of patients who developed a local recurrence was similar between treatment groups (57 years for BCS and 53 years for mastectomy) during the first 5 years. After 5 years of follow-up, the mean age of patients in the BCS group was 46 years between 5 and 10 years and 44 years after 10 years, whereas the only patient who relapsed locally in the mastectomy group after 5 years was 59 years old. These observations are consistent with published evidence for a deleterious effect of age on local recurrence rates after BCS [18–20].

**Comparison of the primary tumour and breast recurrence in the BCS group**

Among the 14 breast recurrences, histological characteristics were not available for one patient. Among the other patients, 10 of 13 recurrences occurred in the same breast quadrant as the primary tumour. The histological features corresponded to those of the primary in nine out of 13 cases. Overall, the site and/or the histological features were akin to those of the primary in eight of 13 cases (62%). The interval between the primary treatment and the onset of the local recurrence was significantly different between concordant and divergent lesions (123 versus 211 months, respectively; \( P = 0.045 \), two-tailed Mann–Whitney test), indicating that early and late recurrences are probably different malignant entities.

**Treatment of breast recurrences and survival after local recurrence**

In spite of excess risk of late local recurrences in the BCS group, the risks of death and metastasis did not differ between the two treatment groups. Indeed, the overall survival rates after local recurrence were similar between the two groups of treatment. These rates at 5 and 10 years were 75% and 65% in the BCS group, and 78% and 67% in the mastectomy group.

**Local recurrence and CBC rates in the IGR database**

As the number of patients included in the randomised study was small, we examined the local recurrence and CBC rates in the described population of the IGR database. Results were similar (Figure 3) to those concerning patients in the trial (Figure 2). In this population, we further analysed the treatment effect according to age for local recurrence and CBC (Table 3). A major difference in local recurrence was observed between treatments (36% versus 12%, 15-year rates) in the younger patients (≤40 years), as shown in Figure 4. In this subgroup of patients, the risk of local recurrence after 5 years was 12-fold higher in the BCS group than in the mastectomy group (\( P = 10^{-6} \)). This risk was only three-fold higher for the older patients (≤41 years) and this difference was also highly significant (\( P = 10^{-6} \)).

**Discussion**

Current results on BCS series do not question the safety of this treatment [8]. However, interest should now be directed to long-term results. In spite of the limited number of patients, the current trial has the advantage of having a mean follow-up of 22 years. Our main finding is that the late local recurrence rate is higher among BCS patients than among mastectomised patients. A significant interaction exists between this parameter and the duration of follow-up. The first 5 years are rather in favour of the BCS approach, but after 5–10 years, an excess of local recurrence is observed. This is not really surprising if published mastectomy
and BCS series with a long follow-up are considered. Indeed, the previously reported experience of the IGR [21] and the Stockholm Breast Cancer Group [22] showed that the local recurrence rate stabilises after 10 years of follow-up (with $\sim 10\%$ for the irradiated patients and 25–30% for the non-irradiated patients) among subjects treated with total mastectomy. Similar figures were found in the EBCTCG material [23]. In contrast, series with a long-term follow-up for BCS [6, 10, 18, 24] show that there is no stabilisation of local recurrence rates after 10 or 15 years. We previously described [25] an annual local recurrence rate of 0.8%, which is compatible with the findings of our trial.

Van Dongen et al. [6], in a large randomised trial including patients with T1 and T2 tumours, showed a higher incidence of locoregional recurrence at 10 years in the BCS group (20%) than in the mastectomy group (12%). It could be contended that these results concerned patients with tumours $>2$ cm macroscopically. However, our own results indicate that the long-term effect on local recurrences also exists for smaller tumours.

If this long-term effect is real, it must be determined whether local recurrences are true recurrences of the primary or new ipsilateral breast cancers. Some arguments are in favour of the second possibility: (i) the local recurrence rate and the CBC rate were similar (Figure 2); (ii) the younger age at diagnosis of patients with a late local recurrence could indicate a radiation-induced carcinogenic effect; and (iii) the mean time between diagnosis of the primary and a breast recurrence was significantly longer for patients whose recurrence exhibited a different histology and/or was in a different quadrant as compared with the primary.

However, the other hypothesis is equally feasible: (i) most recurrences occurred in the same quadrant as the primary and they

Figure 2. (A) Local recurrence rate ($P = 0.0001$, Cox model) and (B) contralateral breast cancer rate ($P = 0.34$, Cox model), according to treatment groups. BCS, breast-conserving surgery.

Figure 3. (A) Local recurrence and (B) contralateral breast cancer rates in the Institut Gustave-Roussy (IGR) database 1954–1983, excluding the current trial patients, for patients with a macroscopic tumour measuring $\leq 2.5$ cm treated with breast-conserving surgery (BCS) or mastectomy.
had corresponding histological features; (ii) the diagnosis of local recurrence may have simply been delayed in the BCS group. This second possibility is in accord with the lower incidence of local recurrence in this group during the first 10 years of follow-up. Smith et al. [26] analysed a series of 1152 patients treated with BCS and radiotherapy and found 136 ipsilateral breast recurrences. According to the tumour location, histological subtype and flow cytometry findings, they classified ipsilateral recurrences as true recurrences or NPMs. The 15-year rate was 6.8% for true recurrences and 13.1% for NPMs. More interestingly, an increased incidence was only observed for the latter tumours after 10 years of follow-up. Our trial results are in accord with their findings.

More recently, two large randomised trials [11, 12] have reported long-term results, but the definitions of local recurrence and the methodology used are not comparable with ours. For instance, in the National Surgical Adjuvant Breast and Bowel Project trial [11], tumours in the ipsilateral breast after tumorctomy were not considered as recurrences when compared with the group of patients treated with total mastectomy.

Our results (Table 3 and Figure 4) confirm that a young age at the diagnosis of primary breast cancer is a strong prognostic factor for local recurrence in the BCS series and not in patients treated with total mastectomy [12, 19, 26–29]. If these results are corroborated, younger patients should be informed of the higher risk of local recurrence when BCS is chosen. The present results do not show a deleterious effect in terms of overall survival or distant metastases; on the contrary, they rather favour the breast-conserving approach. However, recent studies have shown that an excess of local recurrences may subsequently increase the incidence of distant metastasis and eventually lead to a decrease in overall survival [22, 30, 31]. Knowledge of the long-term local results of BCS should not necessarily discourage specialists or patients from choosing this option. However, a major effort should be envisaged so that breast recurrence can be diagnosed early in these patients, through more regular long-term follow-up and probably more frequent recourse to new diagnostic tools such as magnetic resonance imaging and imaging-guided biopsies [32] when indicated by baseline clinical or imaging examinations.

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References