

Analysis of local and regional recurrences in breast cancer after conservative surgery

E. Botteri^{1*}, V. Bagnardi^{1,2}, N. Rotmensz¹, O. Gentilini³, D. Disalvatore², B. Bazolli¹, A. Luini³ & U. Veronesi^{3,4}

¹Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan; ²Department of Statistics, University of Milan-Bicocca, Milan; ³Division of Breast Surgery, European Institute of Oncology, Milan and ⁴Scientific Directorate, European Institute of Oncology, Milan, Italy

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Background: A minority of patients treated conservatively for breast cancer will develop local or regional recurrences. Our aim was to determine how their occurrence may be linked to the evolution of the disease.

Patients and methods: We analyzed 2784 women treated for early-stage breast cancer by quadrantectomy and whole-breast irradiation in a single institution. We evaluated the prognostic factors associated with local, regional and distant recurrences and the prognostic value of local and regional recurrences on systemic progression.

Results: After a median follow-up of 72 months, we observed 33 local events, 35 regional events and 222 metastases or deaths as first events (5-year cumulative incidence 1.1%, 1.2% and 7.6%, respectively). Size, estrogen receptor status, Her2/Neu and Ki-67 were associated with all three types of events, while axillary status and vascular invasion were associated only with the occurrence of metastases or death. Young age increased the risk of local recurrence. Local and regional recurrences were associated with an increased risk of systemic progression: hazard ratios 2.5 [95% confidence interval (CI) 1.1–5.8] and 5.3 (95% CI 3.0–9.5), respectively.

Conclusions: Local and regional recurrences after breast-conserving surgery are rare events. They are markers of tumor aggressiveness and indicators of an increased likelihood of distant metastases.

Key words: breast conservation, local recurrence, regional recurrence, prognostic factor

introduction

Survival of early-stage breast cancer patients after breast-conserving surgery and breast radiotherapy is equivalent to survival after mastectomy [1–4], and today breast conservation is considered the treatment of choice for early-stage breast cancer worldwide. Nonetheless, a minority of patients treated conservatively will develop a local recurrence, which remains one of the greatest concerns in breast-conserving surgery. It can provoke serious anxiety in the patient and, when treated by mastectomy, negate the objective of conservation. Moreover, local recurrence is a marker of tumor aggressiveness and has been linked to an increased risk of distant metastases and death [5–11]. These questions raised the attention on the need to identify more robust pathologic and molecular predictors of local recurrence and more effective treatment strategies that could decrease the risk of local failure after breast-conserving therapy.

In this study, we collected data on 2784 women treated for an early-stage breast cancer by quadrantectomy and whole-breast radiotherapy in order to determine which factors might

predispose the patient to local recurrence, regional recurrence and metastases or death and to determine whether some of these factors had a different effect on the different types of events. We then examined how the local and regional recurrences were associated with the systemic progression of the disease.

patients and methods

study population

We analyzed the data of 2784 women hospitalized at the European Institute of Oncology (IEO) in Milan between 1 January 2000 and 30 June 2003 for a first primary early-stage breast cancer and treated with a quadrantectomy followed by whole-breast irradiation. Neoadjuvant treatments and bilaterality represented exclusion criteria. Following surgery, all cases were discussed during the weekly multidisciplinary meeting attended by surgeons, medical oncologists, radiation oncologists and pathologists. The decision for adjuvant systemic treatment was made on the basis of biological features, staging, treatment previously received and comorbidities. Women were usually followed up by physical examination every 6 months and mammography with or without breast ultrasound (US) annually. In symptomatic cases or when clinically indicated, bone scan, chest X-ray, liver US or computed tomography scan were carried out.

This study was conducted on the basis of the data linkage from two databases: (i) the IEO Breast Cancer Database, a prospective data collection

*Correspondence to: Dr E. Botteri, Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti, 435, 20141 Milano, Italy. Tel: +39-02-57489820; Fax: +39-02-57489922; E-mail: edoardo.botteri@ieo.it

constantly checked for consistency on a weekly basis and used at the multidisciplinary meetings described above, resulting in a proposal for postoperative adjuvant treatments; (ii) the IEO Tumor Registry, a database activated in March 2006 with the aim to collect and analyze data on all those consulting at IEO, at risk of developing or already presenting with a tumor; among other features, it collects all events for the duration of follow-up, allowing multi-stage analyses as the one reported in the present study.

definitions of end points

Local recurrence was defined as recurrence in the original tumor bed with the same histopathologic features of the primary tumor. Regional recurrence was defined as a metastatic disease in the ipsilateral axillary, internal mammary or supraclavicular or infraclavicular nodes, with or without involvement of the ipsilateral breast tissue. Metastasis or death was defined as the presence of metastatic disease in all other locations or death without recurrence, whichever occurred first.

statistical methods

First-event-specific cumulative incidence curves for local recurrence, regional recurrence and metastasis or death were estimated according to methods described by Kalbfleisch and Prentice [12]. New ipsilateral breast tumor, contralateral breast tumor and other non-breast primary tumor were considered as censoring events. In the absence of any of these events, the observation time was censored at the last follow-up visit. The overall survival distribution was estimated using the Kaplan–Meier method.

The prognostic impact of several factors on event-specific cumulative incidence was evaluated one variable at a time, using Gray's test [13]. Variables reaching a *P* value <0.05 in the univariate analysis were regressed on the cause-specific hazard, using multivariate Cox proportional hazards model. The effect of each factor was expressed as hazard ratio (HR) with 95% confidence intervals (CIs). The homogeneity of HRs among local recurrence, regional recurrence and metastasis or death was assessed using methods described by Putter et al. [14]. When the homogeneity assumption was not rejected, a combined estimate was reported.

In a subsequent analysis, the role of local and regional event on distant metastasis or death was estimated by fitting a Cox regression model, in which the local and regional recurrences were represented as time-dependent covariates.

All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (<http://cran.r-project.org/>) with *cmprsk* library developed by Gray (<http://biowww.dfci.harvard.edu/~gray>). All reported *P* values were two-sided.

results

Median age was 53 years (range 23–86). Median follow-up was 6 years (range 0.2–9), with 81.1% of patients having a follow-up ≥ 5 years. Table 1 shows the characteristics of the cohort: 2069 women (74.3%) had a tumor ≤ 2 cm in diameter, 1665 (59.8%) had a node-negative disease, and 1373 (49.3%) had both. Two thousand two hundred and six women (85.7%) had an estrogen receptor (ER)-positive disease.

Five-year overall survival was 96.6% (Figure 1). We observed 33 local recurrences, 35 regional recurrences and 222 metastases or deaths (193 metastases, 24 deaths from breast cancer and five deaths from other causes) as first events, corresponding to a 5-year cumulative incidence of 1.1%, 1.2% and 7.6%, respectively (Figures 2 and 3). Seven regional recurrences of 35 (20%) were found together with the involvement of the ipsilateral breast tissue. Median time to local and regional recurrences was 4 and

Table 1. Study population characteristics

| Variable | Classification | Total no. (%) |
|-------------------------------------|----------------------|---------------|
| All patients | | 2784 |
| Age (years) | <35 | 113 (4.1) |
| | 35–49 | 904 (32.5) |
| | 50–64 | 1249 (44.9) |
| | ≥ 65 | 518 (18.6) |
| Menopause ^a | Pre | 1093 (39.6) |
| | Peri/post | 1670 (60.4) |
| pT | pT1mic | 27 (1.0) |
| | pT1a | 143 (5.1) |
| | pT1b | 539 (19.4) |
| | pT1c | 1360 (48.9) |
| | pT2 | 668 (24.0) |
| | pT3 | 15 (0.5) |
| | pTX | 31 (1.1) |
| pN | pN0 | 1665 (59.8) |
| | pN1mi | 241 (8.7) |
| | pN1 | 556 (20.0) |
| | pN2 | 169 (6.1) |
| | pN3 | 135 (4.9) |
| | pNX | 18 (0.7) |
| Histotype | Ductal | 2141 (76.9) |
| | Lobular | 269 (9.7) |
| | Mixed ductal–lobular | 102 (3.7) |
| | Other | 272 (9.8) |
| Estrogen receptors ^a | Negative | 367 (14.3) |
| | Positive | 2206 (85.7) |
| Progesterone receptors ^a | Negative | 846 (32.9) |
| | Positive | 1727 (67.1) |
| Grading ^a | G1 | 609 (22.9) |
| | G2 | 1306 (49.1) |
| | G3 | 744 (28.0) |
| Her2/neu ^a | Overexpressed | 355 (13.1) |
| | Not overexpressed | 2348 (86.9) |
| Ki-67 ^a | <20% | 1375 (53.8) |
| | $\geq 20\%$ | 1180 (46.2) |
| Vascular invasion ^a | Absent | 2043 (77.0) |
| | Present | 393 (14.8) |
| | Extensive | 217 (8.2) |

^a Information is not available for all the patients.

3 years, respectively. Other first events were seven ipsilateral new breast tumors, 45 contralateral breast tumors and 88 non-breast primary tumors. They were followed by three, five and 17 metastases or deaths, respectively.

Table 2 shows the univariate analysis of prognostic factors. ER status, grading and Ki-67 had a prognostic value on local recurrence, regional recurrence and metastasis or death. Size of tumor >2 cm and overexpression of Her2/neu were significantly associated with metastases or death and borderline significantly with local and regional recurrences. Nodal status and vascular invasion were associated with metastases or death, while age predicted local recurrences.

In the multivariate analysis, reported in Table 3, age remained a statistically significant prognostic factor for local recurrences. Size of tumor, Her2/neu and ER status had no statistically different impact on the three types of events;

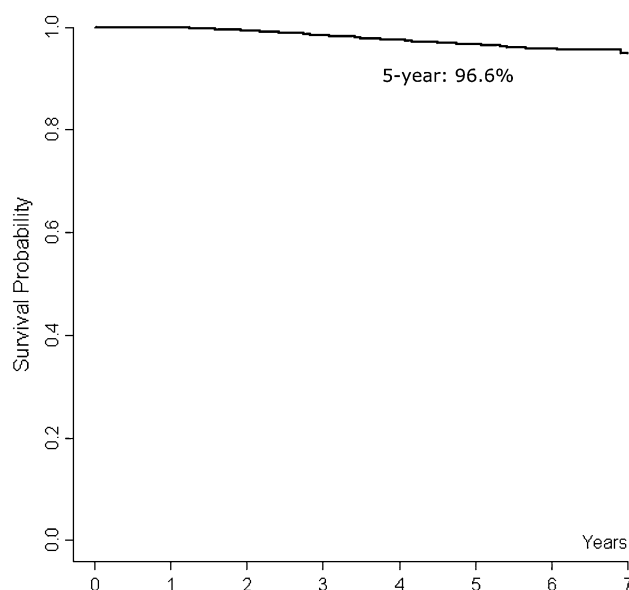


Figure 1. Overall survival.

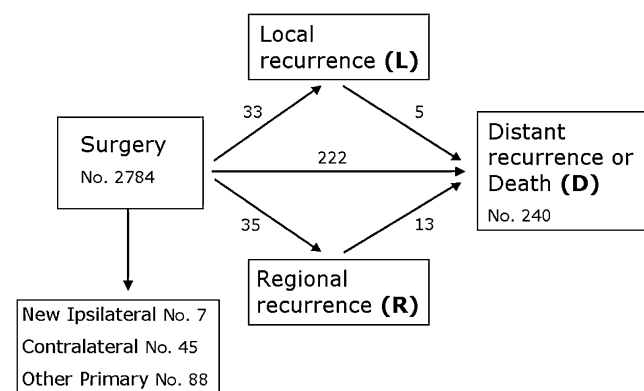


Figure 2. A graphical representation of the multi-stage model.

therefore, a single HR was reported, respectively: 2.0 (95% CI 1.5–2.5), 1.6 (95% CI 1.2–2.1) and 1.5 (95% CI 1.1–1.9). Ki-67 had a similar significant impact on local and regional recurrences (HR 2.0, 95% CI 1.2–3.4), and an even greater impact on distant metastases or death (HR 3.2, 95% CI 2.2–4.6). Nodal status and vascular invasion had no impact on local and regional recurrences, while they were predictors of distant metastases or death (HR 2.4, 95% CI 1.8–3.3 and HR 1.6, 95% CI 1.2–2.1, respectively).

With regard to the prognostic value of local and regional recurrences, 5 women of 33 with local recurrence and 13 women of 35 with regional recurrence had a subsequent distant recurrence (Figure 2), with a corresponding 5-year cumulative incidence after recurrence of 21.7% and 50.9%, respectively (Figure 4). Furthermore, both local and regional recurrences had a significant impact on the occurrence of distant metastases or death, with an HR of 2.5 (95% CI 1.1–5.8) and 5.3 (95% CI 3.0–9.5), respectively. These HRs were borderline significantly different ($P = 0.066$).

Finally, the time elapsing from primary surgery to local or regional recurrence was an additional independent prognostic

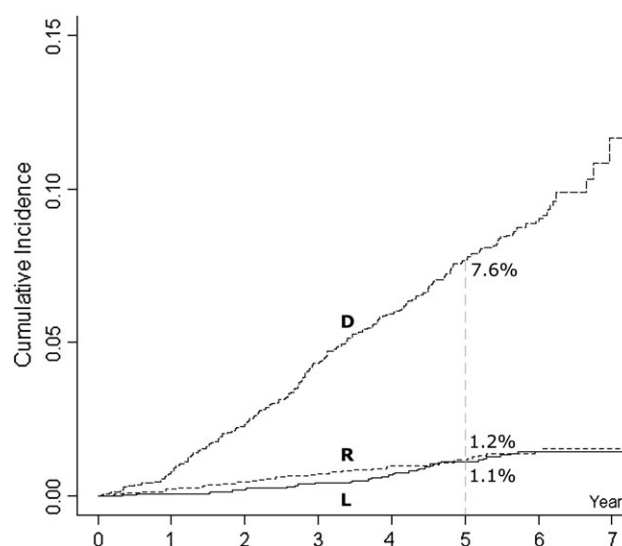


Figure 3. Cumulative incidence of first events. L: local recurrence; R: regional recurrence; and D: distant metastases or death. Percentages are calculated at 5 years.

factor of systemic progression. After adjusting for the type of recurrence, whether local or regional, the risk of metastasis or death decreased linearly with increasing time to relapse ($P = 0.003$). The risk of metastases or death for patients who had a recurrence in the first 2 years after surgery was estimated to be 3.2 (95% CI 1.8–5.5) that of patients who developed a recurrence later on.

discussion

The revolution that surgical treatment of breast cancer has undergone during the past decades has led to the progressive reduction of the extent of surgery [1–4, 15, 16]. Consequently, the quality of life has improved and women are now more motivated to follow screening programs for early diagnosis of the disease. The greatest concern in breast-conserving surgery remains the local recurrence, which can provoke serious anxiety in the patient and, when treated by mastectomy, negate the objective of conservation. In the present series, we observed a very low incidence of local recurrences, with a cumulative incidence of 1.1% at 5 years. This important result highlights the unequivocal improvement of the conservative approach in local control achieved in the last few years.

It is important to distinguish between true local recurrences, originating in the proximities of the primary tumor from residual cancer cells, and new primary tumors arising in the ipsilateral breast. These two types of events may have different biologic behavior and prognosis, since a second primary tumor is a new disease independent of the primary tumor, while a true recurrence denotes a persistent, radioresistant, drug-insensitive and potentially more dangerous disease [17]. In our series, 33 ipsilateral breast tumor recurrences (IBTR) of 40 (82.5%) were classified as true local recurrences, in accordance with previous reports [18].

Even if rare, local failure has been linked to an increased risk of distant metastases and death [5–11]. Our study confirms this

Table 2. Univariate analysis of prognostic factors for first events

| Variable | Classification | Local recurrence | | Regional recurrence | | Distant metastasis or death | |
|---|-------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|
| | | Events (5 years cum inc) | P value | Events (5 years cum inc) | P value | Events (5 years cum inc) | P value |
| All | | 33 (1.1) | | 35 (1.2) | | 222 (7.6) | |
| Age (years) | <35 | 3 (2.5) | 0.02 | 1 (0.8) | 0.94 | 16 (10.5) | 0.15 |
| | 35–49 | 19 (1.7) | | 12 (1.2) | | 86 (8.3) | |
| | 50–64 | 9 (0.7) | | 16 (1.1) | | 88 (6.8) | |
| | ≥65 | 2 (0.5) | | 6 (1.6) | | 32 (7.6) | |
| Size ^a (cm) | ≤1 | 9 (1.1) | 0.08 | 4 (0.5) | 0.08 | 7 (1.1) | <0.01 |
| | 1.1–2 | 10 (0.6) | | 18 (1.2) | | 97 (6.3) | |
| | >2 | 12 (1.9) | | 12 (1.8) | | 113 (16.8) | |
| Number of positive lymph nodes ^a | 0 | 17 (0.9) | 0.57 | 26 (1.5) | 0.10 | 79 (4.7) | <0.01 |
| | 1–3 | 10 (1.1) | | 4 (0.3) | | 70 (8.1) | |
| | ≥4 | 5 (1.9) | | 4 (1.5) | | 73 (23.5) | |
| Histotype | Ductal | 28 (1.2) | 0.77 | 30 (1.4) | 0.38 | 184 (8.3) | 0.68 |
| | Lobular | 3 (0.8) | | 2 (0.4) | | 22 (7.7) | |
| Estrogen receptors ^a | Positive | 19 (0.8) | <0.01 | 21 (0.8) | <0.01 | 154 (6.6) | <0.01 |
| | Negative | 12 (2.9) | | 11 (3.2) | | 64 (16.7) | |
| Grading ^a | G1 | 1 (0.1) | <0.01 | 3 (0.4) | 0.06 | 9 (1.4) | <0.01 |
| | G2 | 13 (1.0) | | 16 (1.1) | | 68 (4.3) | |
| | G3 | 15 (1.9) | | 4 (2.1) | | 132 (18.2) | |
| Her2/neu ^a | Overexpressed | 8 (2.5) | 0.05 | 7 (2.2) | 0.14 | 65 (17.3) | <0.01 |
| | Not overexpressed | 24 (0.9) | | 27 (1.0) | | 155 (6.3) | |
| Ki-67 ^a | <20% | 12 (0.6) | <0.01 | 15 (0.6) | <0.01 | 99 (4.7) | <0.01 |
| | ≥20% | 18 (2.4) | | 16 (2.7) | | 113 (17.8) | |
| Vascular invasion ^a | Absent | 24 (1.0) | 0.62 | 25 (1.1) | 0.97 | 125 (5.6) | <0.01 |
| | Present | 4 (0.9) | | 5 (1.4) | | 50 (12.6) | |
| | Extensive | 4 (2.0) | | 3 (1.6) | | 43 (20.9) | |

Cumulative incidences for local events were compared by the Gray test.

^a Information is not available for all the patients.

Table 3. Multivariate analysis of prognostic factors for first events

| Variable | Local recurrence HR (95% CI) | Regional recurrence HR (95% CI) | Distant recurrence or death HR (95% CI) |
|---|---------------------------------|------------------------------------|--|
| Age: <50 years | 3.2 (1.5–6.6) | | 1.0 (0.8–1.3) |
| Size: >2 cm | | 2.0 (1.5–2.5) | |
| Axilla: positive | | 1.0 (0.5–2.1) | 2.4 (1.8–3.3) |
| Estrogen receptors: negative | | 1.5 (1.1–1.9) | |
| Her2/neu: overexpressed | | 1.6 (1.2–2.1) | |
| Ki-67: ≥20% | | 2.0 (1.2–3.4) | 3.2 (2.2–4.6) |
| Vascular invasion: present or extensive | | 0.9 (0.5–1.6) | 1.6 (1.2–2.1) |

The effect of each factor was expressed as hazard ratio (HR) with 95% confidence interval (CI). The homogeneity of HRs among local recurrence, regional recurrence and metastasis or death was tested. When the homogeneity assumption was not rejected, a combined estimate was reported.

result, with a risk of systemic progression of 2.5 for women with local recurrence in comparison to women without it. However, local recurrence should not be considered as a failure of conservative approach or responsible for systemic progression by itself: previous randomized trials have shown that groups of patients with a high incidence of local recurrences have the same overall survival as that of patients with a low rate of local recurrence [1, 2]. A plausible interpretation is that local recurrence is a marker of tumor aggressiveness and an indicator of an increased likelihood of distant metastases. In addition,

patients with a regional recurrence were at a higher risk of metastases or death than patients with a local recurrence, confirming the recent results of two studies from the National Surgical Adjuvant Breast and Bowel Project node-positive and node-negative protocols [6, 11].

Time to recurrence was a significant prognostic factor of systemic progression, as shown in several published studies [5–8, 11, 19, 20]. In another study [21], we showed how time to IBTR after breast-conserving surgery, besides being a robust prognostic factor of disease reappearance, could play an

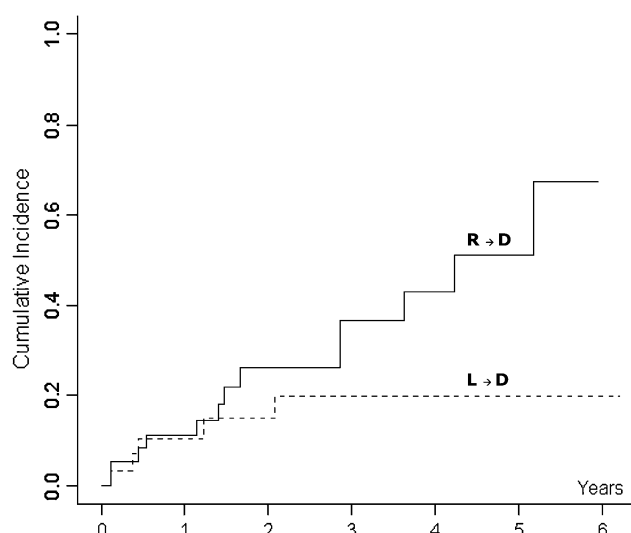


Figure 4. Cumulative incidence of metastases or deaths after local and regional events. (L → D: distant metastases or death after a local event; R → D: distant metastases or death after a regional event.)

important role in the decision of the surgical approach, whether a mastectomy or a second breast-conserving surgery. We could identify a subset of patients, specifically those with a small (≤ 2 cm) and late IBTR (>48 months after surgery), who might be treated with a further conservative procedure, allowing a good local control.

Local, regional and distant recurrences shared some prognostic factors among the characteristics of the tumor, such as tumor size, Ki-67, Her2/neu and ER status. In contrast, positive nodal status and presence of vascular invasion were predictors of systemic progression only, specifically denoting a greater metastatic capacity. Moreover, in accordance with several studies demonstrating that young women have an increased risk of IBTR [22–27], we also found an increased risk of local recurrence for younger women. Although some authors have attempted to elucidate the exact mechanism concerning this relationship, possibly correlated to differential treatment strategies or biological features of tumors depending on age [5, 6, 22, 27], the question remains controversial.

A limitation of our study concerns the duration of follow-up. A substantial proportion of events occurs after 5 years of follow-up, supporting the need for longer follow-up [1, 6, 11].

This is the first study conducted on the basis of the data from the IEO Tumor Registry, which was initiated in March 2006. We strongly believe that a well-structured and centralized tumor registry is a necessary tool for every institution willing to do research. It will in fact allow clinicians and researchers to systematically extract data on subgroups of individuals or tumors of interest and efficiently monitor the hospital activity. Furthermore, the collection of all oncologic events, and not only the first one, is a powerful source of data when studying the evolution of the disease through different stages of severity.

In conclusion, local and regional recurrences after breast-conserving surgery are very rare events. They are markers of

tumor aggressiveness and indicators of an increased likelihood of distant metastases. However, local, regional and distant recurrences are partially independent events, since some prognostic factors differ.

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