Prognosis for Isolated Skin Recurrence after Breast Cancer Treated by Mastectomy

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Abstract. Isolated skin recurrence after mastectomy (ISRAM) for breast cancer is a rare event for which treatment is difficult and subject to debate. Patients and Methods: The records of 75 patients presenting with ISRAM were reviewed retrospectively. The factors liable to affect recurrence prognosis were analyzed, and included both factors related to the primary tumor and its treatment and those related to the recurrence itself. Results: The size of the primary tumor is correlated with the inflammatory nature of the recurrence as well as overall survival. Metastatic lymph node involvement also affects the risk of inflammatory recurrence and is correlated with overall survival. Salvage mastectomy for local recurrence after primary breast-conserving surgery followed by ISRAM has a poor prognosis in terms of recurrence-free survival, and chest wall radiotherapy after primary mastectomy reduces the risk of metastatic development after ISRAM. When confronted with ISRAM, 2 factors affect prognosis: the inflammatory nature of the recurrence impairs overall survival and chest wall radiotherapy reduces the risk of secondary systemic disease. Conclusion: these results underline the importance of good local control when treating the primary tumor (to reduce the risk of ISRAM occurrence, and improve its prognosis if it occurs) and the advantage of locoregional and systemic treatment in the presence of ISRAM and in particular its inflammatory presentation.

The natural history of breast cancer treated by mastectomy is recovery or recurrence in the form of local or local and distant metastases. Local isolated skin recurrence (i.e. with no detected concomitant metastatic disease) after mastectomy (ISRAM) is still a rare event whose frequency is estimated at 5.2% to 9% (1, 2). It gives rise to two problems with no clear solution. The first problem relates to treatment in the absence of a current consensus on management and the diversity of clinical situations, and the second relates to prognosis (3). This paper reviews 75 records of patients presenting with ISRAM who were treated at the Eugène Marquis Comprehensive Cancer Center, Rennes, analyzing the prognostic factors of skin recurrence.

Patients and Methods

A retrospective study was conducted based on 75 records located using data software developed by the Eugène Marquis Comprehensive Cancer Center, covering patients presenting with ISRAM who were treated at the Eugène Marquis Comprehensive Cancer Center in Rennes from 1976 to 2006. The data were taken from consultation and operating room records, and histology results.

ISRAM was defined by the first-time appearance of one or more nodules embedded in the skin of the hemithorax after mastectomy (region limited by the collarbone superiorly, the posterior axillary line laterally, the sternum interiorly and the submammary fold inferiorly).

The parameters analyzed were the initial clinical features at the time of primary breast cancer treatment, the histological features of the primary tumor and its treatment, the clinical features of skin recurrence and its treatment, and disease development.

The mean age of patients on initial diagnosis of cancer was 47.4 years (26 to 89 years, median 46 years). A family history of 1st or 2nd degree breast cancer was found in 29.33% of patients, and 12% had a previous history of fibrocystic mastopathy.

The histological type of the primary tumor was (a) invasive ductal carcinoma (57%), (b) invasive lobular carcinoma (11%), (c) invasive carcinoma associated with an in situ component (29%), and (d) carcinoma in situ (3%). According to the TNM classification, there were 31% of T1, 31% of T2, 9% of T3 and 4% of T4 lesions, with 36% of N1 patients.

Mastectomy was directly performed in 54.7% of patients and as second-line therapy in 45% of cases in the event of local recurrence after primary conservative treatment. Radiotherapy was administered to 73% of patients, either after systematic tumor resection or after primary mastectomy, in the case of a bulky lesion (exceeding 5 cm, pT3), or skin invasion (pT4). Adjuvant treatment following initial systemic treatment with chemotherapy or hormone
therapy in patients with a tumor expressing estrogen receptors was administered to 67% of the women enrolled in the study.

Skin recurrence was observed after an average period of 7.38 years (from 6 months to 30 years, with a median of 6 years) revealed by: (a) a single nodule in 45% of cases, (b) 2 or more in 52% of patients. A clinical inflammatory syndrome was observed at the recurrence site in 13 patients, 3 of which had carcinomatous lymphangitis.

ISRAM management varied in the absence of recommendations: (a) abstention from surgery in 35% of cases, (b) contact excision for diagnostic purposes in 37% of cases, (c) wide-margin surgery in 28% of patients, requiring latissimus dorsi skin-muscle flap coverage in 5 patients. Thoracic radiotherapy was administered to 21% of patients and systemic treatment to 91% of women with chemotherapy or hormone therapy by tamoxifen.

ISRAM development was marked by locoregional relapse (axillary extension, thoracic skin tissue, pectoralis major muscle, homolateral axillary lymph nodes) in 67% of cases, and systemic recurrence in 58% of patients. Median overall survival was 16 years, and median survival after ISRAM 8 years. (Figure 1a and 1b).

The statistical study was conducted on SAS® 9.1 software (Ts1M3, SAS Institute Inc., Cary, NC, USA). The qualitative variable description was estimated on a percentage with a confidence interval of 95% based on normal or binominal distribution depending on numbers. The variable description was based on the population mean and standard deviation. For comparison purposes, the tests were performed with a decision threshold of p<0.005. The percentages were compared with the Chi method or Fisher test depending on numbers. Means were compared using the Student t-test or an ANOVA test in the case of normal distribution or Kruskall-Wallis tests in the case of non-normal distribution. To investigate the link between 2 quantitative variables, the Pearson or Spearman correlation coefficient was calculated together with the slope of the regression line. The Kaplan-Meier method was used for the survival calculation (event=death regardless of cause). The chosen comparison test was the log-rank test with a threshold of p<0.005.

Results

Both the initial parameters related to the primary tumor and its treatment, and the parameters of the ISRAM affecting its prognosis were analyzed.

Initial factors related to the primary tumor. Two such factors had a significant impact on the history of ISRAM. These were the size of the primary tumor, graded using the TNM classification, and the existence of axillary lymph node metastases. The other factors analyzed (age, family history, fibrocystic disease, presence or absence of estrogen hormone receptors in the tumor, SBR histological grade, systemic treatment) did not affect ISRAM. The type of recurrence was significantly correlated with tumor size. A larger proportion of inflammatory recurrences was observed in the case of bulky primary tumors (Table I). Overall survival after ISRAM was correlated with primary tumor size (Table I): it

<table>
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<th>Table I. Nature of skin recurrence and overall survival after skin recurrence depending on primary tumor size.</th>
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<td>T1</td>
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<tr>
<td>Inflammatory recurrence</td>
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<td>Non inflammatory recurrence</td>
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<td>Overall survival (years)</td>
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^1Fisher test.

| Table II. Nature of skin recurrence and overall survival after skin recurrence depending on axillary lymph node status on treatment of primary tumor. |
|-----------------------------|---|---|---|
| pN0 | pN1 | p^1 |
|-------------------------------|---|---|---|
| Inflammatory recurrence | 46 | 16 | 0.001 |
| Non inflammatory recurrence | 2 | 11 | 0.0006 |
| Overall survival (years) | 18 | 11 | 0.0006 |

^1Fischer test.
was 20 years for grade T1, versus 15 years for grade T2, 13 years for grade T3, and 5 years for grade T4. The existence of axillary lymph node involvement at the time of primary tumor treatment (Table II) significantly increased the risk of local inflammatory recurrence, and was correlated with overall survival after local recurrence: overall survival was 11 years in the case of axillary involvement compared to 18 years if the lymph nodes are not involved.

Two factors related to treatment of the primary tumor had a statistically significant impact on the development of ISRAM: (a) recurrence-free survival after local recurrence following a salvage mastectomy after mammary recurrence further to conservative treatment is significantly lower than when a mastectomy was the primary treatment \( (p=0.003) \) (Table III), and (b) radiotherapy performed at the time of treatment of the primary tumor reduces the risk of systemic development after local recurrence post mastectomy (Table IV).

**Prognostic factors of skin recurrence.** Among the factors analyzed, the size of the skin nodule, number of skin nodules, systemic treatment of recurrence, and surgical treatment did not affect the development of local skin recurrence. However, wide-margin surgery tended to improve overall survival without however reaching the point of significance.

Two factors related to ISRAM significantly affected the outcome of skin recurrence: (a) its inflammatory nature, with an overall survival of 7 years in the case of an inflammatory syndrome, versus 17 years in its absence (Figure 2); (b) chest wall radiotherapy in the case of local skin recurrence, which reduced the risk of systemic recurrence (Table V).

**Discussion**

The prognosis of ISRAM depends on factors related to (a) the nature of the primary lesion (large tumor size and metastatic axillary lymph node involvement are risk factors for inflammatory recurrence and impair overall survival after ISRAM), (b) treatment of the primary tumor (ISRAM after a salvage mastectomy leads to poorer recurrence-free survival than ISRAM after primary mastectomy, and primary chest wall radiotherapy reduces the risk of systemic development after ISRAM), (c) the inflammatory nature of ISRAM, and (d) its treatment by radiotherapy, which reduces the risk of metastatic development after recurrence.

Some authors hold primary tumor size to be a factor predictive of outcome of ISRAM. In a series of 249 patients, Fodor (4) observes a 9% risk of local recurrence after mastectomy for pT1, versus 30% for pT2. In 125 patients presenting with 1 to 3 involved axillary lymph nodes, Cheng (5) observes an increased risk of local recurrence for tumors of more than 3 cm. In the same way, Jager (6) judges tumor size and lymph node involvement to be the sole factors predictive of local recurrence after mastectomy. Other authors refute the fact that tumor size affects the risk of ISRAM occurrence. In 1031 patients treated by a combination of mastectomy and chemotherapy, Katz (7) refutes the effect of tumor size of over 5 cm, instead laying claim to pectoral muscle or nipple involvement, and Greco (3) observes a risk of local recurrence after mastectomy of 33% for tumors of 0 to 20 mm, 40% for those of 20 to 40 mm and 8% for lesions exceeding 40 mm. In keeping with the presented observations, Fentiman (1) notes that primary tumor size affects the number of skin nodules without affecting the time prior to ISRAM onset. It is more difficult to assess the effect of lymph node involvement due to the bias caused by adjuvant treatments. Nevertheless, it is acknowledged that primary axillary lymph node involvement is indicative of an aggressive disease, including locally, justifying the need for adjuvant treatment after surgery (2, 8). Thus, for Beenken (9), axillary lymph node involvement affects the risk of local recurrence, and this risk is all the greater when there is marked axillary lymph node involvement. In the presented series of 75 patients, axillary lymph node involvement is also of poor prognosis.
being responsible for a lower overall survival after recurrence and an increased risk of inflammatory recurrence. In patients having undergone chest wall irradiation after mastectomy, Woodward (10) observes lymph node involvement of over 20% of dissected lymph nodes to be a risk factor for local recurrence. Truong (11) observes axillary lymph node involvement greater than 25% to be a factor of local recurrence after mastectomy in his multivariate analysis regardless of whether the patients reviewed were under or over 45 years of age (11). Lastly, in his comparison of the effect of induction and adjuvant chemotherapy in patients treated by mastectomy without irradiation, Buchholz (12) finds the involvement of 4 or more axillary lymph nodes (as well as tumor size in excess of 5 cm) to be indicative for prophylactic chest wall radiotherapy for local relapse.

There is some controversy regarding radiotherapy administered after mastectomy (13). It is sometimes accused of impairing the survival of patients due to cardiac toxicity (14) or, conversely, recommended in particular for patients with a high risk of local recurrence (15-18). In the 3083 patients of the Danish Breast Cancer Cooperative Group randomized to receive adjuvant radiotherapy or not after mastectomy (19), radiotherapy significantly reduces the risk of local recurrence (14% vs 49%) and distant metastases (6% vs 35%). Other authors emphasize its worth. In comparing 2 groups of patients which had or had not received post-surgery chest wall radiotherapy, Woodward (10) observes the benefit of radiotherapy in terms of local recurrence regardless of primary tumor size or lymph node status, although favorable prognostic factors are overrepresented in patients who were not irradiated. Fordor (4) assesses the risk of recurrence in pT1 and pT2 N+ patients to be 8% in the case of irradiation versus 16% in its absence, with respective 15 year-survival rates of 52% and 41%. The literature reports other factors related to the primary tumor affecting local recurrence after mastectomy, such as the existence of multifocal lesions (2, 7), vascular embolus (2, 5, 7, 10), skin or muscle involvement and in this case even with wide-margin surgical resection (7), young age of the patient (5, 11), absence of expression of estrogen receptors (5, 10, 11), and high histological grade (10).

Two prognostic factors have been noted specifically related to ISRAM. These are its inflammatory nature and whether radiotherapy is performed. Other factors affecting survival after ISRAM have been described in the literature. These include the number (1, 2, 20-22) and size (20) of the nodules, vascular embolus and tumor necrosis (20, 23) that can be assimilated to an inflammatory presentation, site of recurrence (24), and finally the disease-free interval after mastectomy (20, 25). The prognosis for inflammatory recurrence of the carcinoma ‘en cuirasse’ type is more difficult to control as it appears to resist a combination of local and systemic treatment (26).

Radiotherapy treatment of ISRAM provides better local control of the disease and seems to have an effect on survival (as observed after primary mastectomy). Several studies show increased survival on isolated local recurrence in patients fully responding to aggressive radiotherapy (27-30). On the other hand, there is little information available about the benefit of secondary chest wall radiotherapy for treating recurrence and the results are contradictory (31, 32).

Regarding other treatments for recurrence, surgical resection alone does not provide satisfactory local control and has no effect on the risk of distant recurrence (33), and the benefit of chemotherapy and hormone therapy appears modest as regards local control (31). ISRAM would appear to be a marker of breast cancer recurrence. In this respect, local control of the primary disease is the principal aim, and is all the more necessary when the primary disease appears to be severe as this affects the risk related to and prognosis after ISRAM. ISRAM occurrence is indicative of an aggressive disease as witnessed by the severity of the inflammatory recurrences, justifying additional treatment to surgery. Here again radiotherapy offers an advantage both locally and at distant sites.

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