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Original article

Role of re-excision for positive and close resection margins in patients treated with breast-conserving surgery

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ABSTRACT

Purpose: To evaluate the incidence of residual disease after additional surgery for positive/close margins and the impact on the rate of local and distant recurrence.
Methods: A retrospective analysis on 1339 patients treated for breast cancer with breast conserving-surgery and radiotherapy at a single Institution between 2000 and 2009 was performed.
Results: During primary surgery 526 patients (39.3%) underwent intraoperative re-excision. At the final pathological report, the margins were positive in 132 patients (9.9%) and close in 85 (6.3%). To obtain clear margins, 142 of these women underwent a second surgery; 35 patients with positive margins (27%) and 40 with close margins (47%) did not receive additional surgery because of different reasons (patients refusal, old age, comorbidity or for focal margin involvement). At second surgery, residual disease was found in 62.9% of patients with positive margins and in 55.5% of those with close margins. At a median follow-up time of 4 years, local recurrence (LR) rate was 2.9% for patients with clear margins, 5.2% ($p = 0.67$) for patients with unresected close margins and 11.7% ($p = 0.003$) for those with unresected positive margins. The HER-2 and the basal-like subtypes had the higher rate of LR and the luminal A the lowest.
Conclusions: A significantly higher LR rate was found only among patients with positive margins not receiving additional surgery, but not in those with unresected close margins. Positive margins are a strong predictor for LR and need re-excision that can be avoided for close margins.

Introduction

Breast-conserving treatment (BCT) is the standard surgical treatment for early-stage breast cancer [1]. The incidence of local recurrence (LR) after BCT ranges nowadays from 3.5% to 6.5% at 10 years of follow-up [2]. Since nearly all LR occur at the site of previous excision and have the same histology as the primary tumor, early LR can be attributed to residual disease at the time of lumpectomy [3]. For this reason, margin status has been considered the most important predictor of LR.

Moreover, the observation that even mastectomy does not completely prevent LR, indicates that aggressive biology and the pattern of growth of the tumor are also risk factors for LR [4]. Furthermore, young age is considered an independent prognostic factor for LR after BCT [2,5]. In the last years, attention has been focused also on the risk of LR related to molecular subtypes [6]. In patients who underwent BCT, luminal A cancers have the lowest risk of LR whereas basal-like and HER-2 tumors carry the highest LR risk [7]. These findings are observed in patients who underwent mastectomy [7] and in those receiving postmastectomy radiotherapy as well [8]. Data from the literature show that triple negative tumors carry an increased risk of LR, independent of the type of surgery performed [9,10]. Authors agree on the important role of adjuvant treatments in reducing LR rate [6,11]. The introduction of trastuzumab in association to chemotherapy drastically reduced the LR rate in patients with HER2 tumors [12].

While positive margins are an important predictor of LR [13,14], there is no evidence that in case of close or clear margins a wider excision decreases LR. There is no consensus on what can be considered as an adequate surgical margin. A great variability in margin selection was noted in different papers [15]: 1–2 mm, >5 mm or >1 cm. A microscopic definition of negative margin was given by the NSABP as tumor not touching ink [16]. Close margins are variously defined as tumor cells within 1–3 mm of the inked surface [4].

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The aim of this study is threefold: first of all to evaluate the incidence of residual disease after intraoperative and secondary re-excision for positive and close margins; secondly to identify intrinsic tumor characteristics and clinical risk factors related to positive and close margins after primary surgery; third to evaluate prognosis, in terms of local and distant recurrence rate, according to margin status.

Methods

Patients

A retrospective review of the records of 1339 consecutive patients who underwent primary BCT for invasive or in situ breast cancer at our Institution between 2000 and 2009 was performed.

All patients signed a written informed consent allowing that their clinical data and biological material could be used for research purposes.

Data regarding age, menopausal status, tumor size, histology, grading, multifocality, presence of lymphovascular invasion and nodal status were recorded. Estrogen (ER) and progesterone receptor (PgR) status, oncogene HER-2 and Ki-67 expression were also assessed. ER and PgR positivity was defined as receptor expression in more than 1% of tumor cells by ASCO/CAP criteria [17], HER-2 was considered "overexpressed" when IHC score was 3+ (uniform intense membrane staining in more than 30% of invasive tumor cells) or amplification was found at FISH test [18]; Ki-67 index was considered "high" when more than 14% of tumor cells expressed it.

Furthermore, we approximated molecular subtypes by estrogen receptor, progesterone receptor, HER-2 status and Ki-67 index, as follows: luminal A (ER+ or PgR+ and HER-2−), luminal B (ER+ or PgR+ and HER-2+), HER-2 (ER− and PgR− and HER-2+) and basal-like (ER− and PgR− and HER-2−) [19].

Treatment

All patients underwent breast conserving surgery (BCS) (lumpectomy, wide excision or quadrantectomy), up to the pectoral fascia, with subsequent radiotherapy. The sentinel node biopsy was the standard technique for axillary staging of patients with clinically negative nodes; patients with micro or macro metastasis underwent axillary dissection.

All patients received standard radiotherapy (50 Gy whole breast irradiation plus a boost of 10 Gy on the tumor bed); in case of 4 or more axillary lymph nodes involved, the supraclavicular region was also irradiated.

Patients with intermediate/high risk of relapse according to St Gallen criteria [20] received adjuvant chemotherapy, with anthracyclines or anthracyclines-taxanes regimens. Since 2006 all patients with HER-2 overexpression were treated with trastuzumab in association to chemotherapy. Patients with positive hormone receptors were prescribed adjuvant endocrine therapy in accordance to their menopausal status.

Patients underwent clinical follow-up every 6 months in the first 5 years after surgery and every year subsequently.

Margin status

The margin status was determined by the pathologic evaluation of the inked surface. A positive surgical margin was defined as tumor infiltrating the inked edge of the resection, a close margin as tumor seen at 2 mm or less from the inked resection edge and a negative margin as tumor at more than 2 mm from the edge of resection.

Preoperative imaging and intraoperative techniques (wire-guided localization, ultrasound-guided resection, intraoperative specimen radiography, frozen section analysis) are standard at our Institution. Starting in 2006, preoperative magnetic resonance (MRI) was performed in selected cases (patients with dense breast, younger than 50 years old, in those with a preoperative histological diagnosis of invasive lobular cancer (ILC) or in patients likely to have multifocal or contralateral lesions).

In order to obtain clear margins, re-excision was performed during the first surgery in case of positive margins either at frozen sections or at radiologic evaluation of specimen or according to surgeon's clinical judgment. A second surgery was planned in case of positive or close margins at the final pathological report.

In our database, special attention focused on margin status: the need and the number of re-excisions (during or after the primary surgery) to obtain clear margins, the specialist (radiologist, pathologist and/or gynecological surgeon) who indicated to perform it, the margin status after these re-excisions and the final pathologic evaluation of the specimen were recorded.

Statistical analysis

Clinical-pathological characteristics were reported as frequency, mean and range. Qualitative variables were compared by the Pearson's chi square test or with Fisher exact test; quantitative variables were compared by the variance analysis (ANOVA). Normality of the variables distribution was tested by the Kolmogorov–Smirnov test. For non-normally distributed variables, a non parametric analysis was performed using U Mann–Whitney test. Local recurrence free survival (LRFS) and distant recurrence free survival (DRFS) were estimated using the Kaplan Meier method and compared by the log-rank test. Univariate and multivariate analysis were performed in order to investigate which patient and tumor characteristics (age, tumor size, histology, grading, multifocality, histotype, presence of lymphovascular invasion, nodal status, ER and PgR status, oncogene HER-2 and Ki-67 expression) were associated with the risk of having positive margins after primary surgery and if positive resection margins were independent risk factor for the development of local and distant recurrence. Independent variables value was checked with multivariate analysis according to Cox regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are calculated. Statistical analysis was performed using the SPSS 15.0 software for Windows. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

Results

Study population

Clinical and pathological characteristics of patients are summarized in Table 1.

The median follow up was 47.5 months (range 3–93.6 months).

Surgical treatment and residual disease

Of the 1339 women treated with BCS, 526 (39.3%) underwent intraoperative re-excision during primary surgery. Independently from the specialist that gave indication to perform the re-excision, tumor cells were found in 41% of the specimens (9% in situ and 32% invasive tumor cells). If the re-excision was performed according to the radiologist judgment, the re-excision specimen was more often interested by in situ tumor compared to re-excisions indicated by the surgeon or by the pathologist (16% vs 9% both for surgeon and pathologist; $p < 0.05$).