Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC)

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Abstract

Purpose of the study: A retrospective analysis on 1407 patients with invasive ductal carcinoma (IDC) and 243 invasive lobular carcinoma (ILC) was performed in order to compare the histological features, the immunohistochemical characteristics, the surgical treatment and the clinical outcome in the two groups.

Results: ILC seems to be more likely multifocal, estrogen receptor positive, HER-2 negative and to have a lower proliferative index compared to IDC. ILC, when treated with conservative surgery, required more frequently re-excision and/or mastectomy because of positive resection margins. No difference was observed in terms of 5-year disease free survival and local relapse free survival between the two groups, in the whole series and in the subgroup of patients treated with breast-conserving treatment.

Conclusion: ILC can be safely treated with conservative surgery but a more accurate preoperative evaluation of tumor size and multifocality could be advocated, in order to reduce the re-excision rate.

Keywords: Breast cancer; Infiltrating lobular carcinoma; Infiltrating ductal carcinoma; Breast conserving treatment; Breast cancer prognosis; Surgical treatment

Introduction

Invasive lobular carcinoma (ILC) of the breast accounts for 5–10% of all breast cancers. Histologically ILC is characterized by small round cells which grow in single-file and infiltrate the stroma without determining a strong inflammatory response. Because of its distinctive growth pattern and biology, ILC often fails to form distinct masses producing more subtle clinical and radiographic findings. The ability of ILC to elude early detection and the possible underestimation of the disease extent often leads to a more advanced stage on presentation than invasive ductal carcinoma (IDC). Moreover, according to many authors, ILC is more frequently multifocal, multicentric and bilateral. For these reasons, although breast-conserving therapy (BCT) is generally accepted as the standard treatment for breast cancer, concern remains for BCT in case of ILC. Data from the literature on the efficacy of BCT for ILC are controversial. Some studies suggest higher relapse rate after BCT for ILC compared to IDC while others show equivalent outcome.

Several further differences in demographic and tumor characteristics between ILC and IDC are reported. Patients with ILC are generally older at the time of surgery, have larger primary tumors, higher expression of hormone receptors and lower grading than IDC. Furthermore, there is agreement that the organ distribution of metastatic disease tends to be different for ILC compared to IDC. ILC mainly spreads to the gastrointestinal tract and to pelvic organs, while IDC primarily relapses to lungs, pleura and central nervous system.

The purpose of this study is to compare histological features, immunohistochemical characteristics, surgical treatment and clinical outcome in the two groups.
treatment and clinical outcome of ILC and IDC in a group of patients treated at a single Institution.

Materials and methods

Study population

The study is based on 1650 sequential cases of invasive breast cancer (1407 (85.3%) IDC and 243 (14.7%) ILC) treated in our Department between 1999 and 2009.

All patient underwent pre-surgical mammography, clinical examination and breast ultrasonography. All lesions were cytologically or histologically confirmed before surgery. Preoperative MRI was performed since 2006 in all patients with dense breast, young age, suspected multifocal lesion or with a preoperative histological diagnosis of ILC at fine needle/core biopsy.

In our series 183 patients (11% of the total number of patients) underwent preoperative MRI. Of them, 122 were affected by IDC (12% of IDC patients) and 61 by ILC (25% of ILC patients).

Breast conserving-surgery (BCS) followed by radiotherapy (50 Gy whole breast irradiation plus a boost of 10 Gy on the tumor bed) was the treatment of choice for most of the patients; when BCT was contraindicated (because of tumor size or multicentricity) modified radical mastectomy was performed. We considered free margins a distance from the inked surface of >2 mm. In case of mastectomy, radiotherapy was performed only in case of inflammatory breast cancer or if 4 or more lymph nodes were involved. Sentinel node biopsy became the standard treatment for clinically node negative patients at our Institution in 1999; since then, complete axillary dissection was performed only in case of micro- and macro-metastatic sentinel node. Standard adjuvant treatments were prescribed in accordance with international guidelines (antracyclin containing regimens at first and then antracyclin–taxane combinations) or patients were included in randomized trials. Most of the patients with positive axillary nodes, less than 70 years old and without significant morbidity, received adjuvant chemotherapy, followed by endocrine treatment if hormonal receptors were expressed. Node-negative patients received chemotherapy if classified as at intermediate/high risk based on tumor size, grading and age. Since 2006, all patients with tumors over expressing HER2 oncogene received adjuvant trastuzumab in association to chemotherapy. Tumors were considered HER-2 positive if the FISH test was positive or if the Herceptest-score was 3+ (>30% of the cells with mutation) and HER-2 negative if the Herceptest-score was 0–1+ (<10% of the cells expressed the mutation). In case of Herceptest-score 2 (10–30% of the cells expressing the mutation), the FISH TEST was performed.

Median follow-up time was 60 months (range 12–144). The length of follow-up was the same for both subgroups (ILC and IDC patients). Patients underwent clinical follow-up examination every 6 months in the first 5 years after surgery and every year subsequently. Annual mammography was indicated for all women; annual liver ultrasonography and chest X-ray were required for N-positive patients. Bone scan was performed in case of symptoms.

Patients were divided in two groups according to the ductal or lobular histotype. Tumor characteristics, surgical treatment, local relapse free survival (LFRS) and disease free survival (DFS) were analyzed in both groups.

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

Statistical analysis

Statistical analyzes were 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. Quantitative variables were compared by the Pearson’s chi square test. Qualitative variables were compared by the variance analysis (ANOVA). Normality of the variables distribution was tested by the Kolmogorov–Smirnov test. For nonnormally distributed variables, a nonparametric analysis was performed (U Mann–Whitney test). A logistic regression model was used for multivariate analysis. Hazard ratios (HRs) are present with their 95% confidence intervals (CIs). DFS and LRFS curves were estimated using the Kaplan Meier method and compared by the log-rank test.

Results

Clinical and biological characteristics

In the present series, ILC in comparison to IDC is more likely to be multifocal, estrogen receptor (ER) positive, progesterone receptor (PgR) positive, HER-2 negative and with lower proliferative index and grading. Table 1 summarizes the clinical and pathologic tumor characteristics of ILC compared to IDC subtype.

Surgical treatment

No significant difference was observed between the IDC and the ILC group in the initial surgical approach, being BCS the treatment of choice for most of the patients. Our standard treatment policy is in fact based on variables not including histotype.

In the ILC group, margins of resection were more frequently involved/close at the pathological report on permanent sections. As a consequence, in a significantly higher percentage of patients with ILC a second surgery (conservative reexcision/mastectomy) was needed in order to obtain negative margins.

Overall, there was no difference in the total number of mastectomies performed for ILC and IDC (Table 2).

At multivariate analysis, only plurifocality and tumor size (but not histotype, grading, age, ER and HER-2 status)
were found to be independent predictors for reexcision, conferring a two-folds risk (Table 3).

Relapse risk and survival analysis

The 5-year DFS was similar in the IDC and ILC group (79% vs 83%, p = NS) (Fig. 1). Also the 5-year LRFS was comparable in the two groups (94% vs 96% respectively, p = NS).

In patients with tumor diameter <20 mm (T1), the 5-year DFS was not significantly longer for ILC compared to IDC (89% vs 87%, p = NS). No difference was observed in the 5-year DFS for patients with ILC and IDC tumors larger than 20 mm (T2–3) (77% vs 76% respectively, p = NS).

Stratifying by nodal status, the 5-year DFS both for node-negative disease (N0) and node-positive disease (N1) was not different for patients with ILC compared to those with IDC at any T stage (92% vs 90% for N0 disease and 83% vs 75% for N1 disease; p = NS).

As to patients who underwent BCT, no difference was observed in the 5-year DFS between ILC and IDC (89% vs 85%, p = NS). Also the 5-year LRFS was similar for IDC and ILC patients (95% vs 96% respectively, p = NS). Furthermore, 5-year DFS was similar in patients with ILC and IDC treated with BCT, independently from tumor size (90% vs 89% for T1 tumors and 89% vs 75% for T2–3 disease; p = NS).

A multivariate survival analysis was performed with a Cox regression model: larger diameter at diagnosis, nodal involvement, ER-negative status and HER-2 amplification (but not histological type, high grade, high proliferation index or PgR-negative status) were found to be independent predictor factors of shorter DFS (Table 4).

Pattern of relapse

In our series, a trend for ILC to relapse more frequently than IDC to bones and liver (35.7% and 21.4% respectively vs 27.4% and 16.8%) was observed. On the other hand,
IDC relapses more often to the central nervous system (7.4% vs 0). Due to the small number of events, the differences were not statistically significant.

Discussion

In the present study we compare clinical-pathologic features and long-term outcomes of a large cohort of patients with ILC and IDC.

Clinical-pathological features

Our data are consistent with those of several other studies comparing the clinical and biological features of ILC and IDC.

Patients with ILC were more likely to have tumors of low grade and with low proliferative index, as shown also by others.6,13 The percentage of hormone responsive tumors was significantly higher in the ILC group, as reported by other authors.6,11,12,14,15 Moreover, in this series, a higher proportion of HER-2 negative tumors was found in the ILC group. This data is not consistent with the finding of Arpino.6

To analyze data from patients with an adequate follow-up, our series has been truncated in 2009. As at our Institution trastuzumab became a standard adjuvant treatment for HER2-positive patients in 2006, most of the patients included in the study with an over expression of HER2 did not receive the monoclonal antibody.

Some authors have shown that ILC is more frequently observed in older patients6,9,10: in the current series the same trend was observed (the median age at diagnosis was 60 years for ILC and 58 for IDC) but the difference was not statistically significant.

Because of ILC ability to elude early detection, larger tumor size at diagnosis is reported for this histological subtype.6,11 In this series, ILC was slightly but not significantly larger in size (19.7 mm for ILC and 18.9 mm for IDC). The larger size at diagnosis can be explained by the peculiar histology of ILC: growing in a characteristic single-file pattern, it infiltrates the adjacent stroma without causing a desmoplastic reaction and presenting without micro-calcifications. This particular behavior tends to produce deceitful images on radiological exams, often causing an underestimation of the extent of the disease. Furthermore, in this series, ILC was more frequently multifocal, as reported by others.3 For all these reasons, the invasive lobular histology is more frequently associated with mammographically occult disease than IDC.9,15 MRI can be a valid additional imaging study in the pre-surgical work-up for patients with ILC, identifying foci of cancer not seen by other modalities.16,17 Preoperative MRI has a higher sensitivity in finding lesions compared with other techniques, especially when high-resolution equipment is employed. For these reasons, the use of MRI in the preoperative planning is a useful tool in the selection of...
patients suitable for BCS. On the other hand, MRI leads to more mastectomies and to additional diagnostic biopsies, resulting in increased patient anxiety and hospital costs. In the present series, MRI was performed routinely since 2006 in selected cases (in patients with dense breast or younger than 50 years old or in patients likely to have multifocal or contralateral lesion or with a preoperative histological diagnosis of ILC).

Surgical treatment

As ILC is often multicentric and difficult to identify radiologically, concern existed on the feasibility of BCT for this histological subtype. In 1975, a report from the National Surgical Adjuvant Breast Project Protocol recommended against BCS for ILC because of its greater likelihood of presenting as multicentric. In literature there are conflicting results in terms of relapse rate after BCT for ILC and IDC. In this series, BCT rate was similar in the ILC and IDC groups but ILC required more frequently a second surgery to obtain negative margins. In fact, in the ILC group the margins of resection were more frequently involved. On the contrary, Moran did not find a significant difference in positive margin rate between ILC and IDC groups when performing BCT. In the present series, no difference was observed in the total number of mastectomies performed for ILC and IDC. After adjusting for size and multifocality, histology did not seem to be a risk factor for reexcision. The same conclusion was drawn by Morrow who matched 349 patients with pure or mixed ILC to 318 patients with IDC. In her study, patients with ILC were more likely to have contraindications to BCT (25% vs 20%), but on multivariate analysis, after adjustments for age and stage, no difference in the surgical approach was found on the basis of the histological type. These findings suggest that the larger size and the plurifocality at presentation of ILC, compared with IDC, may be responsible for the higher rate of reexcision observed in case of lobular histotype.

Clinical outcome

Many studies focused on the relationship between margin status, local recurrence and survival after BCT, in ILC and IDC patients, with contrasting results. Mate reported a lower DFS and overall survival in a small series of ILC patients treated with BCT, and a slight increase of risk of recurrence in the treated breast; nevertheless no attempt was made at the time of surgery to obtain clear margins and only a minority of patients received complete axillary dissection. More recently, several authors found no difference in local recurrence rate, DFS and overall survival between patients with ILC and IDC treated with BCT. In the large series of Arpino, the 5-year overall survival was 85.6% for ILC and 84.1% for IDC (p = 0.64), but most of the patients in the study were treated with mastectomy. Also in the study of Molland no significant difference was observed at a median follow-up of 4.3 years in the rate of local and distant recurrence either in the overall comparison of IDC and ILC, or in patients who underwent BCS. Viale reports similar results at 7.3 years of follow-up.

In the present study, the DFS and the local recurrence rate were similar in the ILC and IDC group, both in the whole series and in the subgroup of patients who underwent BCT, independently from tumor size and nodal status. At a 5-year follow-up DFS was 89% for ILC and of 85% for IDC for patients undergoing BCT. Also the 5-year LRFS of patients treated with BCS and radiotherapy was similar for ILC and IDC patients.

The largest study in literature showed a better 5-year Disease Specific Survival (DSS) for ILC compared to IDC after matching for stage of disease. The advantage in DSS may be related to a higher expression of ER receptors in ILC. In fact the survival advantage for ILC vs IDC was not seen in the ER-negative population. In the current series only tumor size, nodal involvement, ER-negative status and HER-2 amplification were associated with a shorter DFS at the multivariate analysis; histological type did not seem to influence breast cancer prognosis.

Pattern of relapse

A peculiar pattern of metastases distribution is reported in the literature for ILC. Arpino demonstrated that ILC spreads more frequently to ovaries, peritoneum and gastrointestinal tract, while it rarely involves the central nervous system and lungs contrary to IDC. Viale and other authors confirmed these results. In our series, ILC relapsed more often to liver and bones, while IDC relapsed more frequently to the central nervous system. The difference in the metastatic distribution between the two groups was not statistically significant because of the limited number of events.

Conflict of interest statement

All Authors disclaim any financial and personal relationships with other people or organizations that could inappropriately influence their work.

The study did not have any sponsorship.

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