



Review

Extensive pure ductal carcinoma in situ of the breast: Identification of predictors of associated infiltrating carcinoma and lymph node metastasis before immediate reconstructive surgery[☆]



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ABSTRACT

Aim: To identify predictors for infiltrating carcinoma and lymph node involvement, before immediate breast reconstructive surgery, in patients with an initial diagnosis of extensive pure ductal carcinoma in situ of the breast (DCIS).

Patients and methods: Between January 2000 and December 2009, 241 patients with pure extensive DCIS in preoperative biopsy had undergone mastectomy. Axillary staging (sentinel node and/or axillary dissection) was performed in 92% ($n = 221$) of patients. Patients with micro-invasive lesions at initial diagnosis, recurrence or contralateral breast cancer were excluded.

Results: Respectively 14% and 21% of patients had a final diagnosis of micro-invasive carcinoma (MIC) and invasive ductal carcinoma (IDC). Univariate analysis showed that the following variables at diagnosis were significantly correlated with the presence of either MIC or IDC in the mastectomy specimen: palpable tumor ($p = 0.002$), high grade DCIS ($p = 0.002$) and detection of an opacity by mammography ($p = 0.019$). Axillary lymph node (ALN) involvement was reported in 9% of patients. Univariate analysis suggested that a body mass index higher than 25 ($p = 0.007$), a palpable tumor ($p = 0.012$) and the detection of an opacity by mammography ($p = 0.044$) were associated with an increased rate of ALN involvement.

Conclusion: Skin-sparing mastectomy and immediate breast reconstruction (IBRS) has become increasingly popular, especially for patients with extended DCIS of the breast. This study confirmed that extended DCIS is associated with a substantial risk of finding MIC or IDC on the surgical specimen but also ALN involvement. Adjuvant systemic treatment and/or radiotherapy could be indicated for some of these patients after the surgery. Patients should be informed of the rate of 1) complications associated to IBRS that will potentially delay the introduction of systemic or local therapy 2) complications associated to radiotherapy after IBRS.

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Introduction

Pre-operative extensive pure ductal carcinoma in situ of the breast (DCIS) diagnosed by the combination of mammography and

preoperative biopsies are associated with an increased risk of micro-invasive (MIC) or invasive ductal carcinoma (IDC) identified on the post-operative specimen but also with an increased probability of axillary lymph node (ALN) involvement. ALN metastases were found in 0%–14% of patients with a final diagnosis of pure DCIS [1–5]. Between 5 and 14% of patients pre-operatively diagnosed with pure DCISs present a MIC component on the final report [6–8] and the prevalence of lymph node metastases in these patients varies from 0 to 20% [9–22]. Many studies reported that the proportion of IDC on specimen resection from patients with a pre-operative diagnosis of DCIS, ranged from 6% to 41% [1,2,4,5,8–

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10.23–26] (Table 5). As MIC and IDC are frequently identified in patients with extensive DCIS who undergo mastectomy, recommendation have been published to simultaneously perform a sentinel lymph node (SLN) procedure as lymphatic mapping is unreliable after mastectomy [27] and therefore expose women with invasive carcinoma on their final report to the need for an axillary lymph node dissection with an increased risk of morbidity. The presence of IDC and the involvement of axillary lymph nodes are key determinants of breast cancer adjuvant therapy. As most patients with an indication of radical surgery for extended pure DCIS can undergo mastectomy with immediate reconstruction [28], it is of great value to be able to identify on pre-operative features patients at risk for IDC and ALN metastasis. Several clinical settings have been identified: 1) complications related to immediate reconstructive surgery could potentially delay the introduction of systemic therapy, 2) patients with triple negative, *HER2* positive, high grade, lymph node positive tumors should not suffer a delay of their adjuvant systemic treatment, 3) prosthesis-based breast reconstructions followed by radiotherapy are prone to post-operative complications and poor esthetic results. Identification of preoperative risk factors for IDC and ALN metastases would allow to adapt the treatment scheme and to consider the likelihood of adjuvant systemic treatment and/or radiotherapy before starting any reconstructive surgery. At least the surgeon will be able to warn patients with an increased risk of IDC or ALN involvement before the procedure. The aim of this study was to establish risk factors for infiltrating carcinoma and lymph node involvement in patients with an initial diagnosis of extensive pure DCIS, in order to propose the most adequate multidisciplinary treatment.

Materials and methods

Study population

Between January 2000 and December 2009, 241 patients with a pre-operative diagnosis of pure extensive DCIS had underwent mastectomy at Institut Curie, Paris, France. Patients with micro-invasive or invasive ductal carcinoma at initial diagnosis were excluded from our study. ALN exploration with SLN and/or axillary dissection were performed in 221 patients (92%). The SLN procedure was performed with blue patent only. Axillary lymph node dissection was simultaneously performed when the SLN was positive by imprint cytology or frozen section. We considered, as lymph node positivity, macrometastases (>2 mm), micrometastases (<2 mm) and positive tumor cells by immunohistochemistry. A second operation was indicated when either hematoxylin-eosin staining or immunohistochemistry post-operatively revealed tumor cells in the SLN, including isolated tumor cells [29]. Clinical and imaging features including body mass index (BMI), menopausal status, familial cancer history, clinical palpation of the tumor, opacity, microcalcifications, multifocality at mammography were recorded and type of preoperative biopsies (core biopsy, vacuum assisted biopsy or small lump-ectomy). Pathologic features analyzed on pre-operative biopsies (DCIS nuclear grade, presence/absence of necrosis) and on surgical specimens (presence/absence of invasion, tumor size, histological type of invasive tumor, invasion, histological grade, multifocality, multicentricity, lympho-vascular invasion, estrogen receptor status (ER), progesterone receptor status (PR) and *HER2* status were recommended. Estrogen receptor status (ER), progesterone receptor status (PR) and *HER2* status were only obtained on invasive component. The number of positive lymph nodes with macro-metastasis, micro-metastasis and isolated cells were recorded. Tumors were considered to be positive for either ER or PR if at least 10% of the invasive tumor cells in a section showed nuclear staining [30].

Statistical analyses

Number (percentage) described categorical variables; median (range) described continuous variables. Comparisons between groups were performed using a Chi-square or a Fisher Exact tests for categorical variables and a Student's *t*-test for continuous variables. Univariate analysis was performed to investigate association between invasive carcinoma, axillary metastases lymph node and selected variables. *P*-values were considered significant when <0.05. Statistical analyses were performed using *R* software (www.cran.r-project).

Results

Patients and pre-operative characteristics

The patients' characteristics are presented in Table 1. Median age at diagnosis was 51 years (range 28–82 years). BMI was less than or equal to 25 in 186 (77.5%) women and 111 (46%) were menopausal. At diagnosis, the majority of patients had no palpable tumor (199, 83%). The disease was discovered by mammography, with microcalcifications in 233 cases (97%), opacities on mammography in 34 patients (15%). Lesions were unifocal lesions in 153 patients (64%). The preoperative diagnosis was obtained mainly by macro-biopsy (65%). Most tumors were high grade DCIS (126, 53%) with necrosis (154, 74%) on pre-operative biopsy.

Surgery and post-operative characteristics

All patients had a mastectomy. Immediate breast reconstruction (IBRS) was performed in 167 patients (69%) mainly by implant (81%) (Table 1).

ALN staging was performed in 221 patients (92%) with SLN biopsy in 109 patients (45%), ALND in 93 patients (39%) or a combination of both methods in the remaining 19 patients (8%). Twenty patients (8%) had no ALN staging as ALN staging was not systematic when the patient had a lumpectomy following by a mastectomy after for positive margins (Table 2).

Histological examination of the surgical specimen showed 156 DCISs (65%), 35 DCISs with micro-invasion (14%) and 50 DCISs with invasive carcinoma (21%).

DCISs component was of high grade in 128 (54%) tumors, with necrosis in 151 (84%) tumors. Invasive carcinomas were mainly estrogen receptor positive (34, 71%), grade 2 tumors (27, 54%) with lympho-vascular invasion (13, 30%). Eleven (22%) tumors were of Grade 1 and 7 (14%) tumors of Grade 3. Nine (33%) out of the 27 (54% of DCISs with invasive carcinoma) patients tested showed an over-expression of *HER2* (Table 1).

Twenty patients (9%) had a metastatic axillary lymph node. Out of 128 SLN procedure, 11 showed metastases (1 macro-metastasis, 2 micro-metastases and 8 presented positive tumor cells by immunohistochemistry). Out of 50 patients with an invasive carcinoma component, 17 (33%) showed ALN involvement (Tables 1 and 2).

Adjuvant treatment

Thirty-seven (15%) patients received an adjuvant treatment:

- 20 (54%) a single therapy (8 patients received radiotherapy, 11 patients hormonal therapy and 1 patient chemotherapy)
- 17 (46%) a combination of radiotherapy and systemic treatment (chemotherapy and/or hormonal therapy).
- Chemotherapy was delivered in 13 (26%) of 50 patients with final diagnosis of invasive carcinoma. Chemotherapy was associated most of the time to radiotherapy and/or hormonotherapy

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