



## Original article

# Breast conservative surgery for well-differentiated ductal intraepithelial neoplasia: Risk factors for ipsilateral breast tumor recurrence



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## ABSTRACT

**Rational:** We retrospectively analyzed 232 patients affected by well differentiated ductal intraepithelial neoplasia (DIN1c or DCIS G1) treated with conservative surgery without adjuvant radiotherapy.

**Results:** 25 invasive and 18 non-invasive local recurrences were observed (median follow-up 80 months; 5-year cumulative incidence: 12.2%). Seven of the 15 young patients (<40 y) developed local recurrence (2 in situ, 5 invasive). Age <50 (HR 1.89, 95% C.I. 1.01–3.45), multifocality (HR 3.21, 95% C.I. 1.46–7.06), Ki-67 > 7% (HR 2.33, 95% C.I. 1.20–4.55) and surgical margins <10 mm (HR 2.00, 95% C.I. 1.06–3.76) were significantly associated with an increased risk of local recurrence.

**Conclusions:** Young age, multifocality and small margins appeared as clear risk factors of local recurrence in DIN1c (DCIS G1) population. The presence of multiple poor prognostic features warrant a thorough discussion regarding local treatment.

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## Introduction

DIN, the acronym for ductal intraepithelial neoplasia, and traditionally named ductal carcinoma in situ (DCIS), has increased dramatically in incidence worldwide due to the implementation of screening mammography in the 1980s and 1990s [1–3], with one case detected in every 1300 mammography screenings [4].

The term DIN, which has been slowly gaining ground among pathologists [5], was first proposed by Tavassoli in 1998 [6], replacing DCIS and has been used in our institute since 2006 as, in our opinion, it better describes the non-malignant clinical behavior and has a less traumatic impact on women. In this study we will refer to DCIS G1 as DIN1c.

Mastectomy was the standard treatment for low, medium and high-grade DIN until a few years ago, offering an extremely effective control with local recurrence in 1.4% of patients in a large meta-analysis [7,8]. Over the years, mastectomy was replaced by conservative surgery followed by external beam radiotherapy (EBRT) as an integrated component of treatment [9]. Four large randomized clinical trials evaluated the safety of breast conservative surgery (BCS) for DIN, concluding that radiation therapy (RT) significantly reduced the absolute 10-year risk of any ipsilateral breast event (i.e., either recurrent DIN or invasive cancer) by 15.2% (12.9% vs 28.1%  $2 p < 0.00001$ ). After 10 years of follow-up, there was, however, no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality [10].

In accordance with European Institute of Oncology (EIO) internal policy, RT has not been administered to patients who have undergone BCS with a diagnosis of well-differentiated ductal intraepithelial neoplasia (DIN1c formerly DCIS G1) for more than a decade [9,11,12]. This is in line with the Saint Gallen Consensus

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2009 [13], the ECOG trial [14], the Newport Consensus Conference III [15], the National Consensus Cancer Network [16], and the Saint Gallen Consensus Conference 2011 [17].

We performed a retrospective analysis to identify the subgroup of DIN1c patients with higher risk of local recurrence after BCS without EBRT. The identification of clinical-, pathologic- and treatment-related factors might provide clinicians with information to better tailor treatment decisions, trying to distinguish those patients who could have benefitted from radiotherapy or more extended surgery or adjuvant therapy.

## Patients and methods

We collected information through the institutional clinical database on all consecutive breast cancer patients who underwent surgery at the European Institute of Oncology, for non-invasive breast cancer. Between 1996 and 2007, two hundred-thirty-two patients affected by DIN 1c were identified. All patients were treated with BCS without whole-breast RT.

None of these patients had recurrent breast cancer, previous neoadjuvant chemotherapy, previous tumors or prior breast irradiation.

Age at diagnosis, menopausal status, body mass index, diagnostic presentation and adjuvant treatment with hormone therapy were abstracted from the patients clinical notes and operative reports and were input into a dedicated database.

Predominant histologic subtype, surgical margin distance in millimeters (mm), presence of necrosis, presence of microcalcification and extent of DIN (presence of multifocality) were obtained from the pathology reports of the patients' resected specimens. Pathologists generally divide DIN into five architectural histotypes (solid, micropapillary, cribriform, hypersecretory and apocrine), cribriform being (more than 50% of the specimens) the most common histotype in this series, followed by micropapillary and solid.

Microscopic margin evaluation was performed on every case. Margins were defined as negative if no malignant cells were present microscopically at the specimen edges. Conversely, a positive margin contained malignant cells at the cut edge of the breast tissue. For the purpose of this analysis, we compared patients with positive margins, surgical margin distance <1 mm, patients with surgical margin distance  $\geq 1$  and <10 mm and those with surgical margin distance  $\geq 10$  mm.

Necrosis was defined as the presence of a central zone of necrotic debris with karyorrhexis.

Local recurrence was defined as biopsy-proven reappearance of in situ or invasive cancer in the ipsilateral preserved breast and/or regional lymph-nodes. All patients were followed up every six months. No patients were lost to follow up.

## Post-operative preventive medical treatment

Treatment assignments were discussed by a multidisciplinary team on a weekly basis, and overall some differences in treatment selection over the 10-year follow-up period were observed.

As previously mentioned, whole breast RT was not offered to women with low-grade disease. Preventive drug administration to estrogen receptor positive DIN patients has changed during the 11-year period: unless a clinical trial was available, no hormonal therapy was routinely recommended. As Tamoxifen was introduced later, the recurrence rates in these patients can be biased due to shorter follow-up.

However, during the last 5 years, a benefit of low-dose tamoxifen on surrogate end point biomarkers of breast cancer with fewer side effects has been shown in several phase II trials conducted at

the IEO in premenopausal women with DIN [18,19] or in the pre-surgical setting of invasive breast cancer [20]. Depending on the medical history, low-dose tamoxifen (either 5 mg per day or 20 mg once a week) has been offered to ER positive DIN patients since January 2004. No medical treatment was administered to women with ER-negative disease [21].

## Statistical methods

The main study end-point was the evaluation of the risk of developing local recurrence, as a first event, during follow-up.

Time to recurrence was calculated from the date of surgery until the date of first recurrence (local in situ or invasive, loco-regional invasive). Contralateral recurrences (local or invasive) and other primaries were considered as competing events.

When studying the effect of hormone therapy on prognosis, contralateral recurrences were additionally considered as events of interest and other primaries were considered as competing events.

Cumulative incidences were compared across different subgroups by means of the Gray test.

The prognostic effect of variables that were significant at the univariate analysis, was additionally explored by multivariable analysis according to the Cox proportional hazard model. A  $p \leq 0.05$  was considered to be statistically significant.

All analyses were performed with the SAS software (SAS Institute, Cary, NC) and the R software (The R Development Core Team 2004; Free Software Foundation, Boston, MA).

All tests were two-sided.

## Results

Between 1996 and 2007, two hundred-thirty-two patients affected by DIN 1c were identified.

The median age was 52 years (range 29–80).

Median follow-up was 80 months (range: lower quartile 61–upper quartile 111).

The characteristics of the patients are summarized in Table 1.

DIN was detected in 181 (86.6%) cases by mammography (microcalcifications, opacity or distortion). The most common mammographic finding was the presence of microcalcifications in approximately 70% of patients.

Systematic review of histology was not performed. The histologic subtype based on architectural pattern was cribriform in 122 patients (52.6%), micropapillary in 56 (24.1%), solid in 49 (21.1%), apocrine in 4 (1.7%) and hypersecretory in 1 (0.4%).

Necrosis was present in 12 patients (5.2%), microcalcifications in 163 patients (70.3%).

We found two patients with positive margins, 27 (11.9%) patients had a surgical margin distance <1 mm, 28 (12.3%) patients had a surgical margin distance between 1 and 10 mm; 170 (74.9%) patients had a surgical margin distance >10 mm in the final pathology report.

Multifocality was present in 32 patients (15.8%).

Regarding low grade lesions, 98% of patients were ER-positive and, 95% were negative for Her2-neu amplification.

The median Ki-67 value for all the specimens was 7% (range 1–20).

Table 2 summarizes details of hormone therapy received by patients. Of 208 patients with endocrine response disease ( $ER > 0$ ), 98 were treated with adjuvant endocrine therapy, low-dose tamoxifen being the most common treatment administered in 73 patients (74.4%).

Table 3 summarizes details of 57 unfavorable events which occurred among the patients.

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