Is standard treatment of ductal carcinoma *in situ* of the breast (DCIS) overtreatment? A retrospective multicenter study of 450 patients.

Andrea Villasco [1], Viola Liberale [1], Roberta Rosso [1], Marta D'Alonzo [1], Luca Fuso [1], Luca Giuseppe Sgro [1], Riccardo Ponzone [2], Piero Sismondi [1], Nicoletta Biglia [1]

[1] Academic Division of Gynecology and Obstetrics, Mauriziano Hospital, University of Turin, Surgical Department, Turin, Italy; [2] Candiolo Cancer Institute - FPO, IRCCS, Candiolo, Turin, Italy

ABSTRACT

Purpose: The current standard treatment for all cases of ductal carcinoma *in situ* of the breast (DCIS) is full surgical excision with or without postoperative radiotherapy (RT). Is this overtreatment? This study is aimed at appraising retrospectively the outcomes of the therapeutic approaches adopted in DCIS-affected patients and to define whether the standard treatment can be tailored on the basis of immunohistochemistry and surrogate molecular classification.

Methods: 450 patients treated for DCIS between 2006 and 2016 at the Umberto I Hospital of Turin and at the Candiolo Cancer Institute – FPO, IRCCS were enrolled in this retrospective multicenter study. Correlation between treatment received and local recurrence (LR) was analyzed.

Results: The median follow-up was 81 months and the LR rate was 8.22%. Patients treated with breast-conserving surgery (BCS) alone showed a fourfold greater risk of relapsing when compared with those treated with mastectomy (OR 4.61, 1.74–12.20). No significant risk difference was observed between BCS+RT and mastectomy. Sentinel lymph node biopsy was performed in 56.5% of patients treated with BCS and in 98.9% of those treated with mastectomy: the positivity rate was 8.8% for microinvasive DCIS, and 0.4% for pure DCIS. The risk of relapsing was more than halved in patients with hormone receptor-positive DCIS treated with tamoxifen (OR 0.38, 0.19–0.74). The St. Gallen 2013 surrogate molecular subtype definitions were used to categorize the molecular patterns of 105 patients with pure DCIS; this revealed a non-significant trend for triple negative DCIS to relapse more, and sooner, than luminal DCIS.

Conclusions: Current treatment for DCIS allows to LR rates to be kept low. Molecular classification of DCIS appears to be of little help in the everyday management of the disease.

KEYWORDS

Breast cancer, ductal carcinoma *in situ*, local recurrence, endocrine therapy, sentinel lymph node biopsy.

Introduction

Ductal carcinoma *in situ* of the breast (DCIS) is an abnormal proliferation of epithelial cells of the breast ducts that does not exceed the basal membrane. As an effect of the implementation of screening programs, DCIS today accounts for up to 25% of breast tumor diagnoses [1].

A 2006 review that also included studies on DCIS initially misdiagnosed as benign lesions reported that up to 47% of DCIS cases do not progress to an invasive neoplastic form [2]. This suggests that some DCIS might not require treatment. According to the 4th edition of the WHO Classification of Tumors of the Breast (2012) [3], DCIS is characterized by great intertumoral heterogeneity: high, intermediate or low nuclear grades show differences in growth velocity and variable progression potential. At present, however, it is impossible to quantify the progression risk at diagnosis [4]. Thus, the current standard treatment for all cases of DCIS is full surgical excision with or without postoperative radiation therapy (RT) [5]. Breast-conserving surgery (BCS) is widely employed but is still burdened with a high rate of re-intervention. Consequently, in the last few years, an increasing use of mastectomy (MST) as the first surgical option has been observed [6]. Currently, two different tools may be used to determine the best post-operative treatment: the Van Nuys index and a multigene assay called the Oncotype DX® DCIS Score. The former takes into account certain tumoral characteristics shown to be associated with a higher risk of local recurrence (LR): tumor size, surgical margin width, age at diagnosis, histopathologic classification (grading, comedonecrosis). Patients are stratified into three risk groups: low, intermediate and high [7]. The latter tool analyzes a panel of genes related to tumor growth and has been shown to predict the risk of LR in individuals with low-risk DCIS treated

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Contact
Andrea Villasco; andrea.villasco@unito.it
University of Turin, Surgical Department, Turin, Italy
Mauriziano Umberto I Hospital – Largo Turati 62 – 10128 Turin – Italy
(+ 39) 011 5082682

with BCS alone [8]. Therapy tailoring, as a means to de-escalate standard treatment on the basis of risk stratification, has been introduced. Hence, the impact on the long-term prognosis of all therapeutic approaches classically provided for all patients, such as sentinel lymph node biopsy (SLNB), RT and endocrine therapy (ET), have been thoroughly evaluated. This study is aimed at appraising retrospectively the outcomes of the therapeutic approaches guaranteed to DCIS-affected patients in our institutions, and to establish whether the standard treatment could possibly be modified on the basis of immunohistochemistry (IHC) and surrogate molecular classification.

Methods

Patient selection

Of the 651 patients diagnosed with DCIS and treated between January 1st, 2006 and December 31st, 2016 at the Umberto I Hospital of Turin and Candiolo Cancer Institute – FPO, IRCCS, 450 were enrolled in this retrospective multicenter study (Flowchart 1). For each of them the following data were recorded: tumor characteristics, largest radiological size (considering mammography, US and MRI), preoperative histology/cytology, type of surgery, final histology, IHC, adjuvant treatment, type and management of LR. Updated follow-up was available in 94.9% of cases. Since patients in our series underwent surgery between 2006 and 2016, resection margins were considered suboptimal or positive when their distance from the lesion was less than 10 mm or 2 mm according to changing recommendations [9,10]. Sentinel lymph nodes (SLNs) were identified using peritumoral injection of a Technetium-99 marked colloid the day before the planned surgery and then excised under gamma-probe guidance during breast surgery.

Statistical analysis

Cumulative incidence of LR was taken as the primary endpoint: the disease-free interval (DFI) was measured as the time between the first surgery and clinical/radiological appearance of a LR. Cumulative incidence was evaluated using the Kaplan-Meier method; the differences between the curves were analyzed with the log-rank test. The Cox-Regression model was employed to perform a multivariate analysis of the variables shown to be associated ($p<0.05$) with LR at univariate analysis, providing an HR estimate with 95% CI.

Results

The median age at diagnosis was 55 (31-90) years, and the median follow-up time after surgery was 81 (25-156) months. Overall, 354 patients underwent BCS (79%), and the remaining 96 MST (21%). Mastectomy was associated with a larger radiological size of tumor (44.3 ± 25.5 mm MST *vs* 17.9 ± 15.2 mm BCS, $p<0.001$) and younger age at diagnosis (53.3 ± 12.8y MST *vs* 56.9 ± 11.6y BCS. $p=0.008$). For 152/450 patients (33.7%: 5.2% of the MST group, 41.5% of the BCS group),

Flowchart 1 Patient selection process.

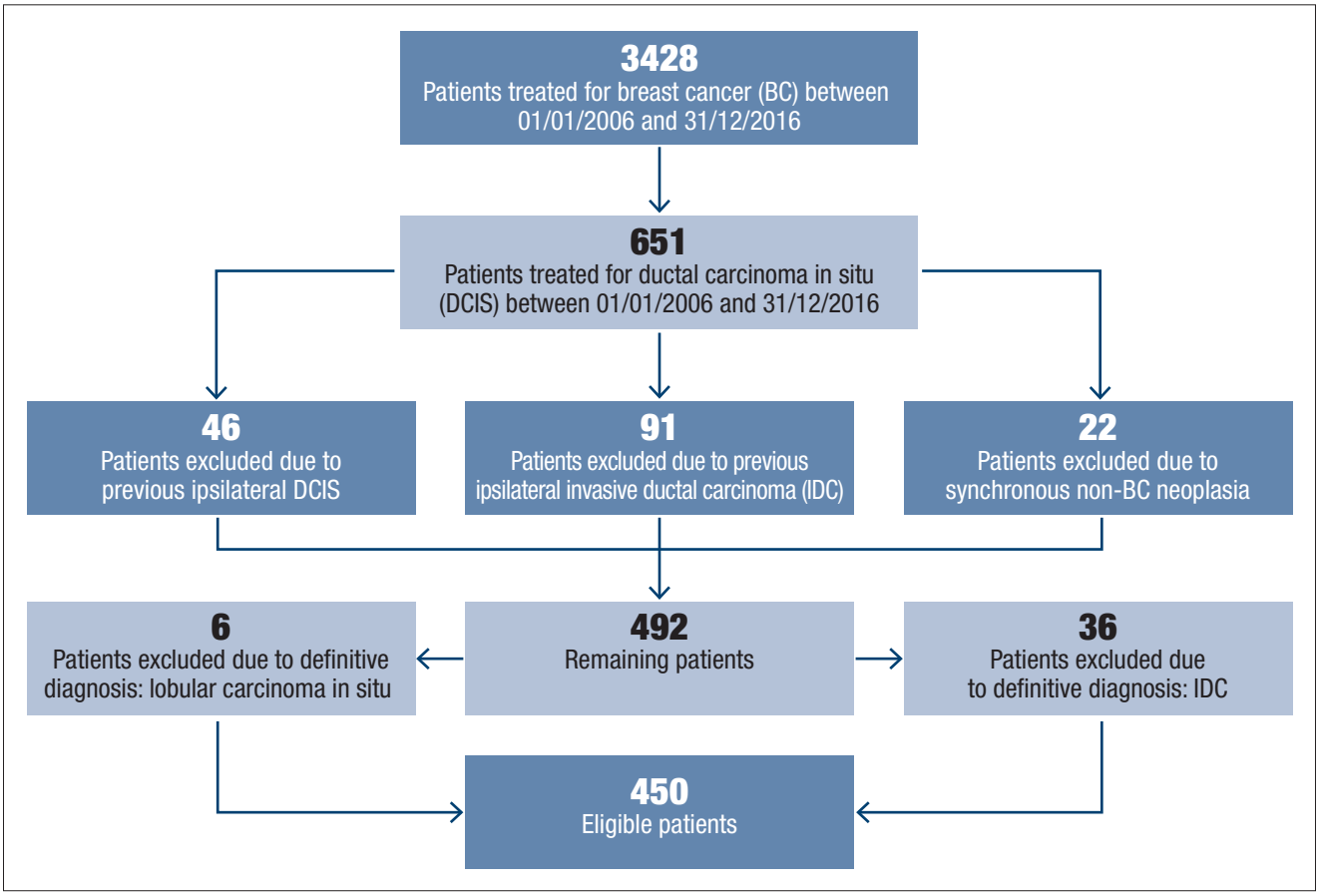


Table 1 Surgery, margins and radiation therapy.

		Mastectomy			Breast-conserving surgery (BCS)		
Re-intervention for positive margins	Re-exc.	0 (0%)			58 (39.5%)	4 (7%)	Marg +
						54 (93%)	Marg -
	Mastec.	0 (0%)			58 (39.5%)	0 (0%)	Marg +
						58 (100%)	Marg -
	None	5 (100%)	0	RT +	31 (21%)	24	RT +
			5	RT -		7	RT -
Final surgery		154			296		
Radiation therapy (RT)	YES	0 (0%)			239 (80.7%)		
	NO	154 (100%)			57 (19.3%)		

Table 2 SLNB.

	Mastectomy		Breast-conserving surgery (BCS)	
	96(21%)		354 (79%)	
	YES	NO	YES	NO
SLNB	95 (98.9%)	1 (1.1%)	200 (56.5%)	154 (43.5%)
PURE DCIS	75 (98.6%)	1 (1.4%)	175 (54.2%)	148 (45.8%)
DCIS MIC	20 (100%)	0 (0%)	25 (86.2%)	6 (13.8%)

the surgical margin width was declared inappropriate on permanent section (2-10 mm, depending on the protocols in force during the periods considered). A complementary surgery was performed in 76.3% of these patients (50% received MST, 50% a local re-excision), achieving adequate margins in 96.5% of cases (4/58 persistent positive margins after re-excision). The remaining 23.7% refused second surgery (previous BCS: 24 patients sent to RT, 7 to follow up; previous MST: 5 patients to follow up). Of the patients treated with BCS, 81% (239/296) accepted the proposed RT on the ipsilateral breast. In no case was RT proposed to patients treated with MST (Table 1). SLNB was performed along with BCS in 56.5% of the patients: it was significantly associated with greater radiological tumor size (28.3 ± 22.8 mm SLNB *vs* 14.2 ± 11.6 mm no-SLNB, $p<0.001$) and high-grade tumors (56% G1 *vs* 84% G3, $p<0.01$). All patients treated primarily with MST underwent SLNB, except one who refused the procedure. A final diagnosis of microinvasion was made in 11.3% of cases: 20.8% after MST, 8.7% after BCS (Table 2). With this approach, information on SLN status was obtained, in a single surgical time, in 91% of cases of pT1mic, with positivity found in 8.8% of cases (4 out of 45 patients: 3 pN0(ITC) + 1 pN1a). In 2/6 pT1mic with missing N data, SLNB was performed in a second surgical time. However, SLNB was also performed in 175 patients with pure DCIS, identifying just 1 case of micrometastasis (in a patient treated with BCS). LR was observed in 8.22% of patients. In 62.2% of the cases, the LR was again a DCIS (median DFI: 42 months), whereas in 37.8% of the cases it was an invasive breast cancer (median DFI: 67.5 months) (Table 3). The LR rate was significantly associated with the type of primary local treatment: 5.2% after MST, 7.9% after BCS+RT, 17.5% after BCS only (Fig. 1). Among the patients treated with BCS alone, the LR rate was found to be increased only in high-grade and intermediate-grade DCIS ($p=0.01$): no patient with low-grade tumor relapsed (Fig. 2). The multivariate analysis confirmed a fourfold greater risk of relapsing for patients treated with BCS alone versus MST (OR 4.61, 95%CI=1.74-12.20). RT after BCS made the risk of LR comparable to that of MST (OR 1.90, 95%CI=0.82–4.41). All patients considered, neither nuclear grade, nor tumor size showed a significant correlation with LR rate, but both were associated with microinvasion ($p=0.05$ and 0.03 respectively). Microinvasion was significantly associated with an increased cumulative incidence of LR, with a threefold greater risk of relapse compared with pure DCIS (OR 3.23, 95%CI=1.48-7.06) (Fig. 3). The St. Gallen 2013 surrogate molecular subtype definitions were used to categorize the molecular patterns of the 105 patients with pure DCIS and full IHC characterization; this showed a non-significant trend for triple negative (TN) DCIS to relapse more and sooner than luminal DCIS (Fig. 4). Only 4 of the 36 patients with suboptimal margins after surgery developed LR. However, we observed a non-statistically significant higher frequency of LR in patients with suboptimal margins who did not receive RT (15.2% *vs* 7.4%) (Fig. 5). After surgery, 77% of the patients with ER-positive DCIS started a tamoxifen (TAM)-based ET: their risk of relapsing was more than halved (OR 0.38, 95%CI=0.19-0.74) compared with that of the 78 patients who refused TAM treatment (Fig. 6).

Table 3 Type of local recurrence.

	pTis	pT1mic
NEW DCIS	18 (62%)	5(62%)
NEW IDC	11 (38%)	3(38%)

Figure 1 Local recurrence: cumulative incidence according to treatment. Green line = BCS alone, yellow line = BCS+RT, blue line = MST.

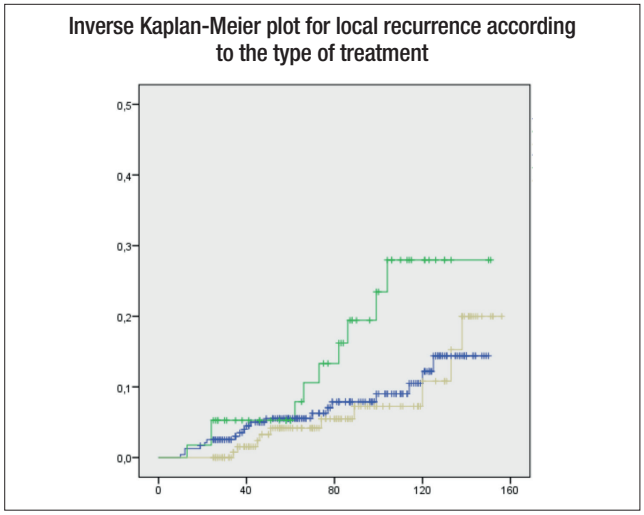


Figure 2 Local recurrence: cumulative incidence in BCS-only patients. Blue line = low-grade DCIS, green line = intermediate-grade DCIS, yellow line = high-grade DCIS.

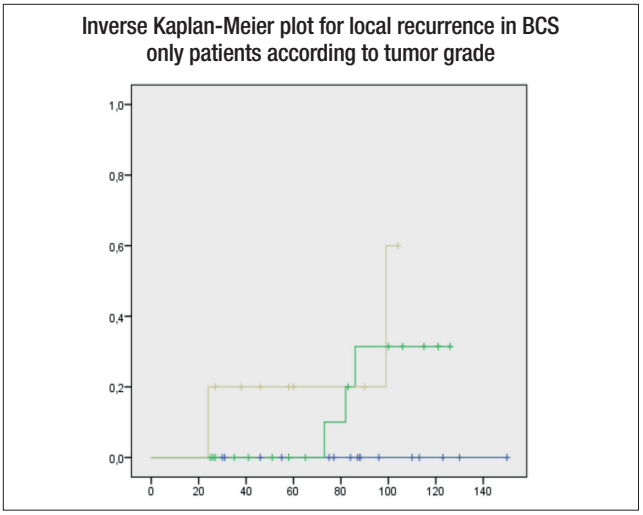


Figure 3 Local recurrence: cumulative incidence according to the presence of microinvasion. Green line = microinvasive DCIS, blue line = pure DCIS.

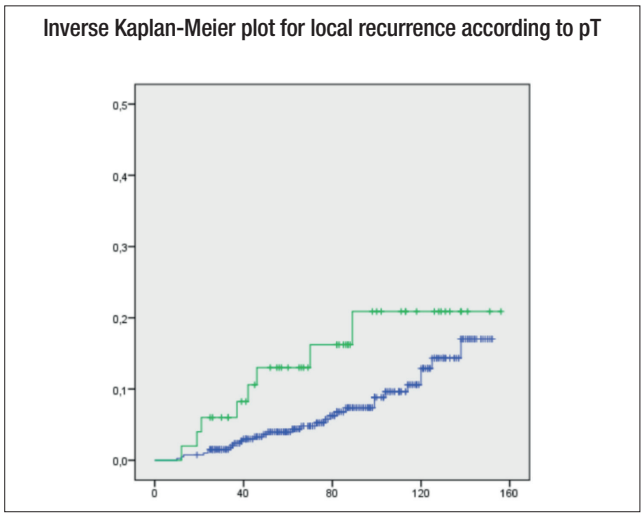


Figure 4 Local recurrence: cumulative incidence according to DCIS surrogate molecular subtype. Blue line = LumA, green line = LumB, yellow line = HER+, purple line = TN.

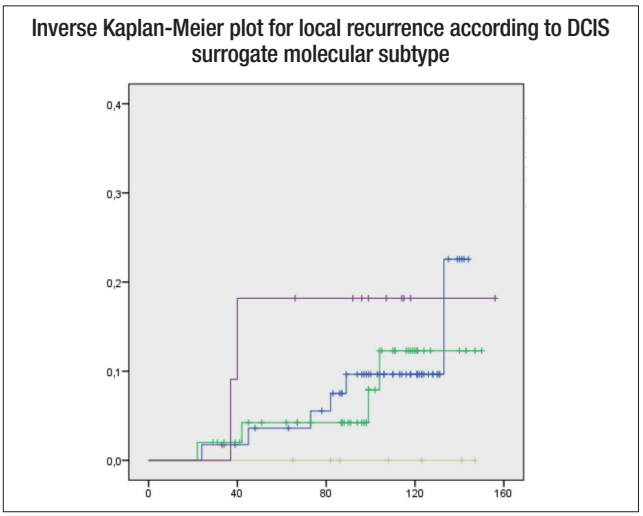


Figure 5 Local recurrence: cumulative incidence in patients with positive resection margins. Green line = BCS alone, blue line = BCS+RT, yellow line = MST.

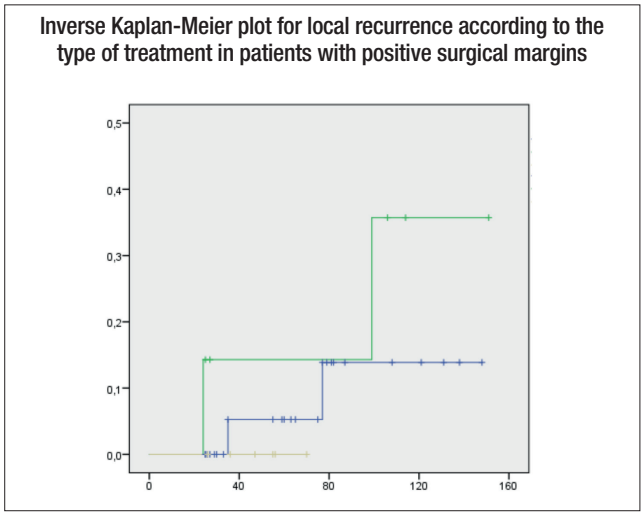
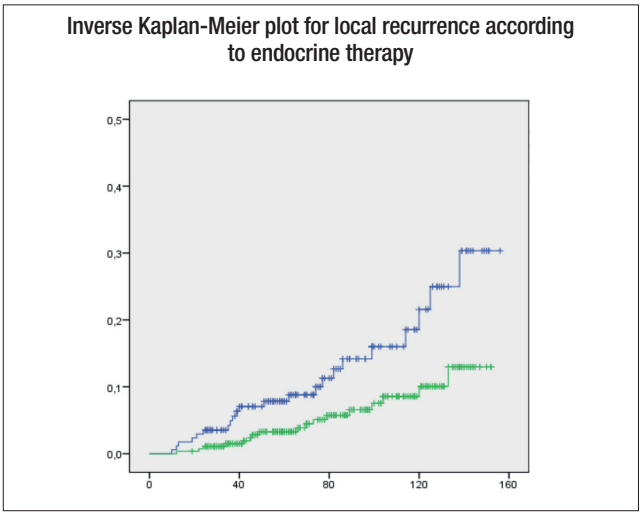


Figure 6 Local recurrence: cumulative incidence according to ET. Blue line = no tamoxifen, green line = tamoxifen.



No difference in LR rate was observed on stratifying the two groups of patients for the tumoral grade. TAM-based ET was not associated with a significant reduction of contralateral new tumoral events in our series (2.3% NO-ET *vs* 3.5% TAM, *p*=0.508) (Table 4).

Discussion

The focus on DCIS overtreatment can be traced back to at least two publications that have shed new light on the natural history of this kind of tumor. The first one, published by Erbas *et al*. in 2006, reported that up to 47% of DCIS (initially misdiagnosed as benign lesions) did not progress to an invasive tumor during 1 to 31 years of follow up, even without any treatment [2]. The second, an observational study published by Narod *et al*. including more than 100000 patients with DCIS of the SEER database, pointed out that the risk of dying from DCIS was low (breast cancer-specific mortality rate 3.3% at 20 years vs 5% from other causes) [11].

Risk factors for LR

At present, it is not possible to accurately predict whether a DCIS will progress to an invasive tumor [4,12]. However, tumoral characteristics associated with an increased LR rate are well known. Lowering the rate of LR is the goal of the treatment of DCIS: an invasive LR, appearing in about 50% of cases, has a negative impact on mortality [13]. A meta-analysis of 44 trials, each including more than 100 patients, published by Wang *et al*. in 2011, showed a strong association of tumoral size, grading, comedonecrosis and margin status with an increased risk of LR [14]. In our series, high-grade tumors showed a non-significant trend to recur as invasive tumors (8.7% for G3 *vs* 3.3% G1 tumors; *p*=0.09). Collins *et al*., in a retrospective study including 3000 patients diagnosed with DCIS who underwent breast surgery, found this association to be statistically significant [15]. Moreover, larger tumor size and high-grade status were significantly associated with microinvasion, which correlates with an increased risk of LR. We did not observe the higher rate of LR of DCIS associated with comedonecrosis that is widely described in the literature. Instead, a significantly lower risk of LR was observed in pure "clinging" and "papillary" patterns (*p*=0.05). In our series, young age at diagnosis was not associated with a higher risk of recurrence. This could be explained by the fact that younger patients were more likely to undergo MST (MST average age=53.3 years *vs* BCS average age 56.9 years, *p*=0.008). Rutter *et al*., analyzing a population of 212,936 women in the USA from 2004 to 2011, observed that the MST rate was significantly higher among younger patients (39.9% among <50-year-old patients *vs* 29.5% among >50-year-old patients; *p*<0.001) [6]. The reasons for this trend are unclear but may be related to the observed high rates of re-excision after BCS as well as to the spread of breast reconstruction surgery techniques ensuring good cosmetic outcomes [16,17]. In our series, DCIS with microinvasion (pT1mic) was associated with a significantly higher LR cumulative incidence than pure DCIS (pTis) (15.7% *vs* 7.3%; *p*=0.04). According to Wang *et al*., pT1mic has an intermediate prognosis, between those of pure DCIS and IDC, as mortality in these patients is about twofold higher (10% at 20 years) than in pure DCIS [18]. This fact may explain the trend in recent years to treat these tumors with a more aggressive approach [19]. "Target therapy" with trastuzumab in patients with pT1mic and HER2-overexpression is currently under evaluation. As reported in a study by Yan Fang *et al*., the disease-free survival (DFS) of patients with pT1mic is significantly lower than that of patients with pure DCIS; while the DFS of HER2+ pT1mic patients is even lower than the DFS of patients with HER2+ pT1A. This latter difference can be ascribed to the undertreatment of patients with HER2+ pT1mic [20].

Table 4 Correlations with local recurrence.

	Local recurrence		*p*-value
	Yes	No	
Surgical Intervention			
Mastectomy	8(5.2%)	146	**0.015**
BCS + RT	19(7.9%)	220	
BCS alone	10(17.5%)	47	
DCIS			
Pure	29(7.3%)	370	**0.039**
Microinvasion	8(15.7%)	43	
ER+ DCIS			
Endocrine therapy	14(5.4%)	246	**0.025**
No endocrine therapy	10(12.8%)	68	
Margins			
Positive + RT	2(8%)	23	**Ns**
Positive - RT	2(18.2%)	9	
Grading			
G1	2(3.3%)	58	**Ns**
G2	9(6.3%)	134	
G3	18(8.7%)	189	
St.Gallen			
Luminal A	4(8.5%)	43	**Ns**
Luminal B	3(6.8%)	41	
HER2	0(0.0%)	5	
Triple Negative	1(11.1%)	8	

Surrogate molecular classification

Different molecular patterns underlie different behaviors of tumoral cells, both in invasive and in microinvasive breast tumors [21]. Complete IHC was available for 105 of our 399 patients with pure DCIS, and hence it was possible to classify them into molecular profiles (Luminal-A, Luminal-B, HER2+ or TN), as described in the St. Gallen Consensus of 2013; [21] we did not observe any significant difference in the recurrence rates, probably because of the small number of patients with HER2+ and TN DCIS. However, TN and Luminal-B tumors showed a non-statistically significant trend to recur earlier than the other molecular subtypes (median DFI 38.5 months and 70 months respectively

vs. Luminal-A 77 months and HER2+ 108 months). In the literature, available data about the usefulness of this classification in DCIS are scarce and inconsistent. In 2013, Zhou *et al*. analyzing 381 patients with DCIS, complete IHC, and a median follow-up of 161 months, did not find any prognostic significance of the molecular classification [22]. In the same year, Sharaf *et al*. got the same result in a series of 94 patients [23]. However, in 2015, Williams *et al*. identified a significantly lower recurrence rate in patients with Luminal-A DCIS, compared with other phenotypes: the HER2 phenotype had the highest risk of recurrence (HR 6.72, 95%CI=2.76-16.4), followed by the Luminal-B (HR5.52, 95%CI=2.38-12.8;) and TN (HR3.82, 95%CI=1.45-10.0) ones. However, only a minority of patients was treated with RT and ET, hence the high rate of LR (over 18%) in this study [24].

Surgery and RT

In our series, LR rates were 5.2% after MST, 7.9% after BCS+RT, and 17.5% after BCS alone; the LR risk in the patients who underwent BCS alone was fourfold greater than that of patients who underwent MST (OR 4.61, 95%CI 1.74-12.20). These data are consistent with those in the meta-analysis published in 2015 by Stuart *et al*., who compared 9391 patients from five prospective and 21 retrospective trials; the LR rate was 2.6% after MST, 13.6% after BCS+RT, and 25.5% after BCS alone (OR 2.61; $p<0.0001$) [13]. In patients who underwent BCS alone, we observed a significantly higher proportion of LR in high-grade versus low-grade DCIS patients; to date, none of the patients with low-grade DCIS has shown LR. This suggests that in low-risk DCIS patients, omitting adjuvant RT could be considered. On the other hand, the results of trials exploring the possibility of avoiding RT after BCS in low-risk DCIS, summarized in a recent meta-analysis, showed that RT almost halved the risk of ipsilateral LR (RR 0.53, 95%CI=0.45-0.62) compared with what was observed in those who did not receive it (absolute risk reduction of 15%: 95%CI=12-17%); conversely, no difference in overall mortality was found (RR 0.93, 95%CI=0.79-1.09) [25]. Our data are consistent with the results of a prospective ECOG group study, which compared 565 patients with low-grade or intermediate-grade DCIS to 105 patients with high-grade DCIS, all undergoing BCS alone. The authors demonstrated that patients with low-/intermediate-grade DCIS with at least 3 mm negative margins have an acceptably low rate of ipsilateral breast events at 5 years after excision without irradiation (6.1%, 95%CI=4.1-8.2%). On the contrary, patients with high-grade lesions have a much higher LR rate (15.3%, 95%CI=8.2-22.5%), suggesting that excision alone is an inadequate treatment in these patients [26].

Margins

A long-standing controversy in the literature concerns the optimal negative margin width for DCIS treated with BCS and whole-breast irradiation (WBRT). Recent guidelines indicate that, in the case of an invasive tumor, the condition of "no ink on tumor" (absence of tumoral cells on the excision margins, demonstrated by inking the surface of the surgical specimen) is adequate to define the margin as "clear" [27]. On the contrary, as far as DCIS is concerned, two meta-analyses have shown opposite results. Wang *et al*., in 2012, found decreasing ORs for LR as the threshold distance increased up to 10 mm, and thus recommended a 10 mm excision margin for DCIS [10]. A more recent meta-analysis, comparing 20 studies with a total of 7,883 patients, recommends a prudential distance of at least 2 mm from the resection margin, as margins larger than 2 mm are not associated with a further reduction of LR probability in women receiving radiation [28]. Based on these results, the 2 mm threshold distance has been accepted as an adequate margin in DCIS treated with BCS + WBRT, as it is associated with low rates of LR, decreased need of re-excision, improved cosmetic outcome, and reduced health care costs [7].

Since the patients in our series underwent surgery between 2006 and 2016, resection margins were considered suboptimal or positive when their distance from the lesion was less than 10 or 2 mm, according to the changing recommendations. In our patients, the status of excision margins, known to be a strong predictor of LR [29-38], did not seem to affect the LR rate, probably because 76.3% of patients with suboptimal margins underwent a second surgery, obtaining clear margins in 96.5% of cases. Only 11 of the 36 patients who still had positive margins (including 5 patients who underwent MST) did not receive RT; among these, we observed 2 relapses: their LR rate, 18.2%, was higher than that of the whole series, i.e., 8.22%, but the difference was not statistically significant.

Endocrine therapy

In our series, women with hormone-responsive tumors receiving adjuvant ET showed a significantly lower incidence of LR, with their risk of relapsing more than halved when compared with that observed in women not taking ET. This result is consistent with the literature. A Cochrane meta-analysis of two randomized controlled trials (the NSABP B-24 and UK/ANZ DCIS trials) demonstrated that TAM after breast surgery reduces DCIS ipsilateral recurrence (HR 0.75; 95%CI=0.61-0.92) and that patients receiving ET have a lower risk of new contralateral breast tumors, both in cases with DCIS (RR 0.50; 95%CI=0.28-0.87) and in those with DCI (HR 0.79; 95%CI=0.62-1.01) [39].

SLNB

The role of SLNB in DCIS is still a matter of discussion. In our series, in accordance with the guidelines in force during the period considered [40-41]. SLNB was performed in patients with larger and high-grade tumors, as well as in patients who underwent MST. Five cases, including four patients with pT-1mic, displayed SNL positivity. The only case of SNL positivity among the patients with pure DCIS was probably due to an incorrect histopathological definition of the tumor or, possibly, to passive translocation of tumoral cells (a theory that is currently gaining increasing support in the literature) [42]. Our results are consistent with the current literature, which suggests SLNB only in patients undergoing MST, because it would not possible to perform it at a later time in case of tumor upstaging on permanent section [43]. On the contrary, SLNB should not be performed "d'emblée" in patients undergoing BCS [44-45], not even in cases with preoperative biopsy showing a suspected invasion (B5c) [46], restricting the procedure only to those patients with microinvasion proved on permanent section [47].

Conclusions

Standard treatment of DCIS is associated with a low risk of LR. Treatment de-escalation with RT omission might be possible in low-risk DCIS; in fact, patients treated with BCS alone show a significantly lower LR rate when diagnosed with low-grade as opposed to high-grade DCIS. This suggests that in low-risk DCIS patients, it might be possible to consider omission of adjuvant RT, but more data are needed. On the contrary, in the case of positive margins, omission of RT leads to an unacceptably high rate of LR. In view of the observed low rates of positivity, the SLNB procedure should not be performed in DCIS patients undergoing BCS, restricting the indication only to those patients with microinvasion proved on permanent section. Endocrine therapy in patients with hormone receptor-positive DCIS appears to lower the LR risk independently of the surgical treatment received and should hence be offered to all eligible patients. Results of studies on the molecular classification of DCIS are controversial, and this classification appears to be of little help in the everyday clinical management of the disease.

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