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Research Article

The Role of Margin Status on Local Recurrence in Microinvasive Ductal Carcinoma of the Breast

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ABSTRACT

Microinvasive ductal carcinoma (MIDC) is an infrequent disease that accounts for about 1% of all breast cancer cases. Controversy on the management is related to the limited information available regarding lymph node involvement, recurrence rate and prognosis of the disease. In this retrospective single-center study, we included all patients diagnosed with MIDC at S. Orsola Malpighi Hospital in Bologna from 2011 to 2020. Demographic and clinicopathologic characteristics were collected and analysed. Furthermore, we analysed the factors related to local recurrence using univariate and multivariate analyses. We identified 57 patients diagnosed with MIDC. The median age at diagnosis was 56. Nuclear grade of the invasive foci was high in 44% of the patients. Estrogen receptors were found to be positive in 40% of patients, HER2 was overexpressed in 35% and 40% of patients had a high proliferation rate. Margin status was negative in 72% of the patients while close in 16 patients. 26 patients received breast conserving surgery (BCS) and 31 underwent mastectomy. Nodal staging with sentinel lymph node biopsy was performed in 82% of cases. In 96% were found negative sentinel lymph node. 92% of patients receiving BCS were treated with combined radiotherapy. 32% were treated with adjuvant endocrine therapy and 28% were given adjuvant chemotherapy. At a median follow-up of 42 months, we had no axillary recurrence, but 3 patients (5%) had local recurrence. In the multivariate analysis close margins are associated with a 16% increase in local recurrence. Results from this study show that sentinel lymph node biopsy could not be useful in MIDC according to the low risk of lymph node metastasis. The rate of local recurrence was 5% and our findings suggested a possible role of margin status in the development of local recurrence.

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Article Summary

We conducted a retrospective single-center study to explore factors related to local recurrence in microinvasive carcinoma of the breast. Our study shows that close margins are associated with an increased probability of local recurrence regardless of biomolecular profile.

Introduction

The widespread application of screening programmes has led to an increased detection of early breast cancers, including microinvasive

ductal carcinoma (MIDC). The concept of 'microinvasion' was firstly introduced by Lagios in 1982 [1]. MIDC is defined as an invasive ductal carcinoma with no focus measuring more than 1 mm according to the 8th edition of AJCC Cancer Staging Manual that first recognized this specific T substage in 1997 [2]. It is an infrequent disease that accounts for about 1% of all breast cancer cases and in most of the cases it is associated with ductal carcinoma *in situ* (DCIS) typically with those with a large extent, comedo-type architecture, and hormone receptor negativity [3-6]. The present literature agrees in describing MIDC as more biologically aggressive than pure DCIS. In fact, MIDC frequently

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has high histologic grade, negative hormone receptors and HER2 overexpression [7-9].

However, lymph node involvement, recurrence rate and prognosis are controversial. Consequently, the appropriate management strategy is still debated. Current guidelines such as National Comprehensive Cancer Network Clinical Practice Guidelines and American Joint Committee on Cancer (AJCC), Eighth Edition, considered MIDC more like an invasive carcinoma than a pure DCIS, recommending treating MIDC as an invasive carcinoma. Many studies agree with this, however other recent studies do not support these recommendations [4, 7, 10-14]. Although most recent studies reported MIDC has a low risk of lymph nodes metastasis in the literature, the axillary lymph nodes involvement ranges approximately from 1,5% to 12,5% and surgical management of the axilla is controversial [8, 9, 13-16].

Also, survival rate greatly differs between different studies. While some reported worse cancer-specific survival compared with pure DCIS, other describe MIDC with favourable prognosis with no significant differences in overall survival and disease-free survival with respect to pure DCIS [4, 7, 10, 13, 14]. Considering this, our purpose was to evaluate axillary lymph node involvement, treatment management and recurrence rate in our cohort of patients and to identify risk factors for local recurrence. In particular, we examine the rate of local recurrence according to the margin status.

Materials and Methods

We conducted a single-institution retrospective study of patients diagnosed with MIDC between 2011 and 2020 treated at the breast surgery department of S. Orsola-Malpighi Hospital in Bologna. MIDC was defined as ductal carcinoma *in situ* with one or more foci of invasive disease each <1mm. We excluded patients previously diagnosed with invasive breast cancer and those treated with neoadjuvant chemotherapy. For all patients we collected the following information: demographic information, clinicopathologic data, diagnostic features, treatment characteristics and clinical follow-up. All patients underwent pre-operative mammography, ultrasound, and diagnostic testing with fine needle aspiration cytology (FNAC) or needle biopsy (Tru-cut biopsy or Vacuum-assisted breast biopsy). Immunohistochemistry studies were performed on surgical specimens. In some cases, the small size of microinvasive foci does not allow pathologists to execute a complete biomolecular profile.

Estrogen receptor (ER) and progesterone receptor (PR) were considered positive if <1% of tumor cells were positive [17]. Tumors were considered HER2+ if they scored 3+ by IHC or scored 2+ and subsequently amplified based on FISH/SISH analysis as stated in the 2013 ASCO/CAP guideline. We used the median Ki67 value of 25%, to distinguish between high and low proliferation rates [18, 19]. Demographic and clinicopathologic characteristics were described using descriptive statistics. We estimated an ordinary least squared (OLS) linear probability model for experiencing a local recurrence over margins' status and controls related to biomolecular profile of the tumor as well as age. And the dependent variable is a dichotomous variable equal to one when local recurrence happens and zero otherwise. The model is briefly described in equation (1) with subscripts referring to patients' individual observations:

$$PMargins_i, Xi=0+1 Margins_i+ 2Xi+ei \quad (1)$$

Where, 'Margins' is our main variable of interest with value 'negative' if >1mm, 'close' for margin <1mm and 'positive' if tumor at ink. 'X' refers to a vector containing a set of control variables while 'e' is the error term. P-value thresholds of <0.01 <0.05 and <0.10 were considered for significance threshold. All statistical analysis was performed using Stata 14 software.

Table 1: Clinicopathological characteristics.

Characteristic	n=57	(%)
Age at diagnosis		
Median (Range)	56 (28-87)	(5)
<= 40	3	(68)
40-49	39	(27)
>=50	15	
Diagnostic features		
Mass-like lesion	17	(30)
Microcalcification	40	(70)
Pre-operative diagnosis		
C5	10	(18)
B3	2	(3)
DCIS	44	(77)
MIDC	1	(2)
Nuclear Grade of invasive foci		
1	11	(19)
2	21	(37)
3	25	(44)
Margins		
Negative	41	(72)
Close (DCIS)	16	(28)
ER Status		
Positive	23	(40)
Negative	18	(32)
Unknown	16	(28)
PR Status		
Positive	14	(25)
Negative	23	(40)
Unknown	20	(35)
HER2 Status		
Positive	20	(35)
Negative	17	(30)
Unknown	20	(35)
Ki67 proliferation index		
<20%	15	(26)
>=20%	23	(40)
Unknown	19	(33)

ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; DCIS: Ductal Carcinoma *In Situ*; MIDC: Microinvasive ductal carcinoma.

Results

I Clinicopathologic Characteristics and Treatments Variables

We identified 57 patients diagnosed with MIBC on final pathology from 2011 to 2020. All patients underwent surgery at our institute. The median

age at diagnosis was 56 (range 28-87). Table 1 shows clinicopathological characteristics of the 57 patients. The majority (70%) of patients showed up with suspicious calcification at pre-operative mammography while only 30% had a mass-like lesion. 10 patients underwent FNAC and had a diagnosis of C5. In 47 cases (82%) we performed core needle biopsy with 44 patients diagnosed with DCIS, 2 patients with B3 and 1 patient with MIDC. Nuclear grade of the invasive foci was high in 44% of the patients. Estrogen receptors were found to be positive in 40% of patients, HER2 was overexpressed in 35% and 40% of patients had a high proliferation rate. Margin status was negative in 72% of the patients while close in 16 patients (28%).

Table 2: Treatment variables.

Treatment Variables	Tmic	
Entire population	n=57	(%)
Surgery type		
Quadrantectomy	26	(46)
Total Mastectomy	18	(32)
SS Mastectomy	8	(14)
NSS Mastectomy	5	(9)
Reconstruction		
Performed	27	(47)
Not performed	30	(53)
Sentinel lymph node biopsy		
Not done	10	(18)
Negative	45	(79)
Macrometastasis	0	(0)
Micrometastasis	0	(0)
Itc	2	(4)
Adjuvant treatment		
Radiation therapy	24	(42)
Chemotherapy	16	(28)
Endocrine therapy	18	(32)
None	16	(28)
Unknown	1	(1)

SS: Skin Sparing; NSS: Nipple Skin Sparing; ITC: Isolated Tumor Cells.

Treatment variables are summarized in (Table 2). 26 patients (46%) received breast conserving surgery (BCS) and 31 (54%) underwent mastectomy: 18 total mastectomies, 8 skin-sparing mastectomies and 5 nipple-skin-sparing mastectomies. Immediate breast reconstruction with tissue expander was performed in 27 cases. Nodal staging with sentinel lymph node biopsy (LSNB) was performed in 47 (82%) of 57 patients. 10 patients who did not undergo lymph node staging had a pre-operative diagnosis of DCIS low grade or breast lesion of uncertain malignant potential (B3). Of 47 patients receiving lymph node biopsy, 2 (4%) were found to have isolated tumor cells in the sentinel node while 45 (96%) were found to have negative sentinel lymph nodes. Of 26 patients receiving BCS 24 (92%) were treated with combined radiotherapy. The decision not to combine radiotherapy with BCS in 2 patients was made after multidisciplinary discussion considering advanced age and multiple comorbidities. The decision to receive adjuvant chemotherapy or endocrine therapy was made by our multidisciplinary team at our weekly meetings and then discussed with the patients. 18 patients (32%) were treated with adjuvant endocrine therapy. 16 patients (28%) were given adjuvant chemotherapy, 15 with a HER2+ cancer were treated with

Taxol associated with Trastuzumab and one with triple negative carcinoma with multiple microinvasive foci was given EC and Taxol.

Table 3: Characteristics of 3 patients who developed local recurrence.

N	1	2	3
Age	52	59	46
Surgery	NSSM	BCS	BCS
SLNB	Negative	Negative	Not Performed
ER	+	-	+
PR	-	-	-
HER2	3	0	3
Ki67	16	24	45
G	2	3	3
Margins	DCIS <1mm	DCIS <1mm	DCIS <1mm
Adjuvant Therapy	None	RT	RT + CT
Recurrence	Paget	CDI Triple	DCIS G3
Histology	Disease with T1mic	Negative	
DFS	33	54	58

NSSM: Nipple-Skin-Sparing Mastectomy; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; RT: Radiotherapy; CT: Chemotherapy; DFS: Disease Free Survival.

II Follow-Up

Median follow-up was 42 months. 3 patients (5%) had local recurrence: one patient had Paget's disease with a single focus of T1mic 33 months after nipple-skin-sparing mastectomy and underwent nipple-areola complex excision. One patient had homolateral recurrence of ductal invasive triple negative carcinoma 54 months after quadrantectomy combined with radiotherapy and underwent mastectomy with sentinel lymph node biopsy and adjuvant chemotherapy. The last patient had homolateral DCIS high grade 58 months after quadrantectomy combined with radiotherapy and adjuvant chemotherapy treated with nipple-skin-sparing mastectomy. Table 3 shows clinicopathologic characteristics and treatment patterns of the 3 patients who developed local recurrence. All 3 patients had close margins with DCIS <1mm. No patients had distance or axillary recurrence.

III Statistical Analysis

Table 4 reports estimates for our linear probability model of local recurrence. Unconditionally on available controls [column (1)], close margins are associated with an 18.8% increase in local recurrence with respect to negative margins. The coefficient is statistically significant at 1% with an R-squared of 14.2%. Controlling for the biomolecular profile of the tumor [column (2)], the point estimate of the coefficient for close margins goes to 0.161 remaining significant at 5%. This translates into a 16.1% increase in probability of local recurrence associated with close margins even after controlling for biological characteristics. Interestingly in this set of estimates, R-squared rise at 31.9 percent. To account for possible concerns related to heteroskedasticity of the error terms, in column (3) we propose estimates with robust standard errors where, despite the small sample size, the coefficient for close margins remains significant at 10%.

Table 4: Estimates Linear Probability Model for Local Recurrence.

	OLS (1)	OLS (2)	OLS with robust SE(3)
Margin status			
Close	0.188*** (0.062)	0.161** (0.065)	0.161* (0.086)
HER2 Status			
Negative		0.025 (0.159)	0.025 (0.141)
Positive		0.010 (0.161)	0.010 (0.191)
PR Status			
Negative		0.204 (0.161)	0.204 (0.161)
Positive		-0.068 (0.159)	-0.068 (0.093)
ER Status			
N		-0.089 (0.164)	-0.089 (0.151)
P		0.125 (0.156)	0.125 (0.101)
Nuclear Grade			
2		-0.015 (0.093)	-0.015 (0.068)
3		0.072 (0.095)	0.072 (0.074)
Ki67 proliferation index (%)			
>=20%		-0.029 (0.194)	-0.029 (0.122)
<20%		-0.022 (0.184)	-0.022 (0.152)
Age at diagnosis			
40-49		0.080 (0.148)	0.080 (0.100)
>=50		0.078 (0.139)	0.078 (0.104)
Constant	0.000 (0.033)	-0.175 (0.171)	-0.175 (0.158)
N	57	57	57
R2	0.142	0.319	0.319

Standard errors in parentheses.

*p<0.1, **p<0.05, ***p<0.01.

Discussion

Controversy on the management of MIDC is related to the limited information available regarding the prognosis of the disease. In the current literature, the role of lymph node biopsy in MIDC is controversial and the rates of axillary lymph node metastasis are highly variable [8, 9, 13, 15]. In this study, SLNB was performed in 82% of cases and the incidence of SLNB metastasis considering all macrometastasis, micrometastasis and ITC was 4% even if in all cases they were ITC. Of particular interest at a median follow-up of 36 months we found no lymph node recurrence in the face of local recurrence. These findings support that SLNB may not be useful in MIDC even considering the possible implication of lymph node staging for systemic

therapies. In our study, adjuvant treatments were mainly decided after multidisciplinary discussion based on cancer biology.

In consistence with rates reported in literature, we had a LR rate of 5% [9, 14, 20]. Our findings indicated a possible role of margin status in the development of LR. In our cohort, close margins are associated with a 16% increase in probability of LR regardless of biomolecular profile. Conversely to other studies we found no statistically significant association between LR and patients' age at diagnosis [20]. Aside from margin status, another possible predictor of LR is the type of surgery performed, although we did not find an association between surgery type and LR risk. In our study one of the three cases who developed a LR was treated with nipple-sparing mastectomy while two underwent BCS with additional radiation therapy. This information could be applied to stress the importance of the use of intraoperative margin status analysis both in patients treated with mastectomy and those treated with BCS. If a close margin is found in BCS, excision of an additional tissue may be easily performed. More complicated is when the closest margin is deep or superficial. A close deep margin should be considered adequate if the BCS or mastectomy are properly performed reaching deeply the pectoralis major muscle's fascia, while if the closest margin is superficial skin excision or conversion to skin sparing mastectomy to total mastectomy should be considered in order to clear the margin.

Several studies have suggested that close or positive margins are associated with LR after mastectomy for pure DCIS while others found no association [18-22]. Anyway, studies specifically focused on the margin status role in MIDC are currently lacking. This retrospective study should be interpreted in light of several limitations. First of all, the small sample size and the short duration of follow-up. Also, the heterogeneity in treatment may have influenced the LR estimates.

Conclusion

Further studies with larger sample size and longer follow-up are needed to establish if positive or close margins are associated with an increased risk of local recurrence specifically for MIDC. Accurate risk estimates are essential to assess margin status and determine the consequent appropriate disease management. The necessity for additional surgical procedures or adjuvant therapies following initial surgery in MIDC with close margins needs to be clarified.

Funding

None.

Conflicts of Interest

None.

Availability of Data

The datasets generated and/or analysed during the current study were available from the corresponding author on reasonable request.

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