Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jan 02; 10(B):104-112.
https://doi.org/10.3889/oamjms.2022.7613
eISSN: 1857-9655
**Category:** *B - Clinical Sciences*
***Section:*** *Oncology*



# National Cancer Institute Experience in Micro-invasive Breast Carcinoma Treatment and Outcome

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**Edited by:** Ksenija Bogoeva-Kostovska
**Citation:** Salama M, Khater A, Adel I, Selim M. National Cancer Institute Experience in Micro-invasive Breast Carcinoma Treatment and Outcome. Open-Access Maced J Med Sci. 2022 Jan 02; 10(B):104-112. https://doi.org/10.3889/oamjms.2022.7613
**Keywords:** Micro-invasive breast carcinoma; Carcinoma *in situ*; ductal carcinoma *in situ*; Breast-conserving surgery
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**Received:** 15-Oct-2021
**Revised:** 01-Dec-2021
**Accepted:** 22-Dec-2021

**Funding:** This research did not receive any financial support
**Competing Interest:** The authors have declared that no competing interest exists


**Abstract**

**BACKGROUND:** Significant relationship between breast cancer immunophenotype and risk of recurrence either local and/or distant may help determine which patients might benefit more from axillary staging and whether axillary staging is warranted in all cases or not. Patients with microinvasive carcinoma can present with axillary lymph node (LN) metastasis, with incidence ranges from 0% to 20%. Thus, sentinel node biopsies are considered for patients with microinvasive carcinoma. The role of axillary staging in micro-invasive breast carcinoma (MIBC) is not well defined, with the rate of axillary LN metastases ranging 0–11%. The present studies focus on the clinical characteristics of MIBC.

**AIM:** The aim of this study was to identify prognostic factors affecting MIBC and evaluate the surgical management, adjuvant treatment for patients with MIBC.

**METHODS:** This is a retrospective study of 139 cases diagnosed with microinvasive breast carcinoma from 2011 to 2015 who were identified in the National Cancer Institute, Cairo University. The pathologic database of our hospital was searched to identify patients with a pathologic diagnosis of MIBC on surgical specimens. The clinical features, sonographic and mammographic images, and pathology records were reviewed.

**RESULTS:** There is increased incidence of MIBC over the past decade. Patients with MIBC were managed surgically with breast-conserving surgery. MIBC has the good prognosis. However, patients who are negative hormonal receptors have relatively substantial risk of relapse within the first 5 years after surgical operation. Adjuvant chemotherapy can only improve the outcomes of patients with negative hormonal receptors.

**CONCLUSION:** Further studies with prolonged follow-up of large cohort are warranted to assess the prognostic significance and treatment of this lesion.

## Introduction

Breast cancer is the most commonly diagnosed cancer in women and the second cause of cancer-related death among women in the United States [1]. The American Joint Committee on Cancer (AJCC 7th edition) defined micro-invasive breast carcinoma (MIBC) as an extension of cancer cells beyond the basement membrane into adjacent tissues with focus ≤0.1 cm in greatest dimension, and AJCC was the first organization to recognize MIBC as pT1mic [2].

Moreover, MIBC, which is one of the rare breast carcinomas, with incidence rate ranging from 0.24% to 3.3% [3]. Moreover, the clinical characteristics, prognosis, and treatments of MIBC are highly controversial [4]. Due to the widespread application of screening mammography, the detection rate of both carcinoma *in situ* (CIS) and MIBC significantly increased in recent years. However, the natural history of cancer cells progression from CIS to MIBC and finally to invasive carcinoma remains unclear, and MIBC may represent the interim stage in the evolutionary progress from CIS to invasive carcinoma [5], [6].

The role of axillary staging in MIBC is not well defined, with the rate of axillary LN metastases ranging 0–11% [7], [8]. Identifying a significant relationship between breast cancer immunophenotype and risk of recurrence either local and/or distant may help determine which patients might benefit more from axillary staging and whether axillary staging is warranted in all cases or not. The present studies focused on the clinical characteristics of MIBC. However, only a few studies have evaluated the survival and treatment, especially adjuvant chemotherapy after surgery, for patients with MIBC [9], [10].

Microinvasion is usually present in high-grade, comedo-type ductal CIS (DCIS) and is less likely to be found in lobular CIS or other types of DCIS [11]. Patients with microinvasive carcinoma can present with axillary LN metastasis, with incidence ranges

from 0% to 20% [12], [13]. Thus, sentinel node biopsies are considered for patients with microinvasive carcinoma. However, the clinical outcome of microinvasive carcinoma remains unknown. While some studies have suggested that the clinical behavior of microinvasive carcinoma is similar to that of DCIS [14], [15], others have shown that clinical outcomes are less favorable in patients with MIBC than in those with DCIS [16], [17]. Thus, no consensus has been achieved with respect to whether MIBC should be treated as a stage 0 DCIS lesion or as a small, invasive carcinoma [18].

The previous studies have reported survival outcome of MIBC patients with conflicted results. Some indicated that CIS and MIBC had similar survival, while others did not [19]. The aim of this study was to identify prognostic factors affecting MIBC and evaluate the surgical management, adjuvant treatment for patients with MIBC.

## Subjects and Methods

### *Patient selection*

This is a retrospective study of 139 cases diagnosed with microinvasive breast carcinoma from 2011 to 2015 who were identified in the National Cancer Institute, Cairo University. The pathologic database of our hospital was searched to identify patients with a pathologic diagnosis of MIBC on surgical specimens. Patients who received neoadjuvant chemotherapy before surgery or who underwent excisional biopsy outside the hospital were excluded. The clinical features, sonographic and mammographic images, and pathology records were reviewed.

The clinical features, including history and clinical presentation, were obtained from the medical records. The clinical history included age, menopausal status, family history of breast cancer, and personal history of breast cancer. The clinical presentation included observation of a palpable mass, nipple discharge, or no symptoms. Ultrasonograms and mammograms were reviewed retrospectively.

### *Pathological analyses*

All pathologic reports were reviewed. A diagnosis of MIBC was rendered when a microscopic focus of invasion ≤1 mm in the longest diameter within an area of MIBC was present [13]. The histopathologic features included the presence or absence of comedo-type necrosis and the nuclear grade. Biological markers including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were examined by immunohistochemical analysis as a routine pathologic assessment in our hospital. ER and PR positivity were defined as nuclear staining in 10% or more of tumor cells. HER2 status was graded as 0, 1+, 2+, and 3+ by immunohistochemistry. HER2 0 and 1+ were considered negative, whereas HER 2 and 3+ were considered positive [19].

### *Evaluating margin status*

Two millimeters (mm) are used by many other institutions and in most publications, so for this analysis, we chose <2 mm as a negative margin for breast conservative therapy (BCT) specimens and mastectomy specimens to permit comparison with other institutional data. Specifically, BCT specimens were routinely oriented and all margins inked accordingly and reported. For mastectomy specimens, the distance to deep margin (fascia) was reported routinely.

### *Treatment*

All patients received either BCT (lumpectomy and whole-breast radiotherapy [RT]) or mastectomy. The decision to perform a sentinel lymph node (LN) dissection or axillary LN dissection was at the decision of the surgeon. The decision to receive adjuvant endocrine therapy (tamoxifen or an aromatase inhibitor), anti-HER-2/neu-targeted therapy, or chemotherapy was made by the treating medical oncologist.

The decision was tailored depending on biological profile of the patient and the tumor, node, and metastasis (TNM) staging. A minimum 5-year follow-up was chosen to allow adequate time for recurrence events.

### *Clinical end point*

The clinical end point was time to first recurrence including local, nodal, or distant recurrence. Regional/nodal and distant metastases were grouped together as a single end point in order to maximize power to detect a significant association between pathologic tumor characteristics, specific treatment modalities, and tumor recurrence.

### *Statistical analysis*

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) versus 21. Age was summarized using mean and standard deviation. Categorical data were summarized as numbers and percentages. Chi-square test was used to compare between the groups with respect to categorical data. Kaplan–Meier method was

used to estimate the recurrence free survival. Predictor variables were related to survival using logrank test. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence (either local or distant metastasis) or last follow-up of the patients. $p < 0.05$ was considered statistically significant.

## Results

### *Clinicopathologic features*

One hundred and thirty-nine breast cancer patients collected retrospectively starting 2011–2015, were diagnosed with MIBC according to the definition by the seventh edition of the AJCC staging manual. All of them were female. The mean age of the patients was 49.5 years with standard deviation 12 and ranged from 23 to 86 years, 49.6% of them were in premenopausal period, 44% in postmenopausal era, and 6.5% in perimenopausal period. Those with positive family history for breast cancer were 21 patients (15%). Breast mass was the most presenting symptom (91%) followed by nipple discharge in 6% (Table 1).

**Table 1: Characteristics of the microinvasive breast cancer patients (n = 139)**

| Characteristics | | Number | Percent |
|---|---|---|---|
| Age* | 49.5 ± 12.1 | | |
| Sex | Female | 139 | 100.0 |
| Menopausal status | Perimenopausal | 9 | 6.5 |
| | Postmenopausal | 61 | 43.9 |
| | Premenopausal | 69 | 49.6 |
| Family history | Negative | 118 | 84.9 |
| | Positive | 21 | 15.1 |
| Presenting symptom | Mass | 126 | 90.6 |
| | Discharge | 8 | 5.8 |
| | Others | 5 | 3.6 |
| Tumor size | T1+Tis | 26 | 18.7 |
| | T2 | 102 | 73.4 |
| | T3 and T4 | 11 | 7.9 |
| LN | N0 | 114 | 82.0 |
| | N1 | 16 | 11.5 |
| | N2 and N3 | 9 | 6.5 |
| Pathology | Invasive duct carcinoma | 130 | 93.5 |
| | Invasive papillary carcinoma | 8 | 5.8 |
| | Invasive lobular carcinoma | 1 | 0.7 |
| Grade | Grade 1 | 2 | 1.4 |
| | Grade 2 | 131 | 94.2 |
| | Grade 3 | 6 | 4.3 |
| Breast surgery | BCS | 54 | 38.8 |
| | MRM | 85 | 61.2 |
| Chemotherapy | No | 19 | 13.7 |
| | Yes | 120 | 86.3 |
| Hormonal therapy | No | 23 | 16.5 |
| | Yes | 116 | 83.5 |
| RT | No | 62 | 44.6 |
| | Yes | 77 | 55.4 |

*The variable is presented as mean±standard deviation, LN: Lymph node, BCS: Breast conservation surgery, MRM: Modified radical mastectomy, RT: Radiotherapy.

### *Breast surgery*

Breast-conserving surgery (BCS) was performed in 54 patients (39%) while mastectomy was performed in the remaining 85 patients (61%).

### *Axillary surgery*

Sentinel LNs (SLNs) were performed to 46 (33%) cases, 36 (78%) of them were free of metastases, and the remaining 10 patients (22%) were positive and proceed to axillary dissection. Axillary dissection was performed in 103 cases, but only 25 patients (18%) had positive axillary LN s and 114 patients (82%) were free of metastases.

### *Pathological outcome*

Pathological tumor size was mainly T2 in 102 cases (73%), T1 in 25 cases (18%), and to less extent T3, T4, and Tis in 9 (6.5%), 2 (1.4%), and 1 case (0.7%), respectively. Ductal carcinoma was the predominant type of microinvasive carcinoma (130/139) (93.5%), and the remaining cases were of papillary type 8 cases (5.8%) and lobular type in 1 case (0.7%). The component was mostly of Grade 2 (131 cases) (94.2%). Six cases had nuclear Grade 3 (4.3%), and 2 cases (1.4%) had nuclear Grade 1 (Table 1).

The tumor biomarkers tested showed heterogeneous pattern of staining, with triple positive in 15 cases (10.8%) staining positive for both ER, PR, and HER2 and triple negative in 19 cases (13.7%) staining negative for ER, PR, and HER2 (Table 2, Figures 1-5).

**Table 2: Biological markers of microinvasive breast cancer patients (n = 139)**

| Characteristics | Number | Percent |
|---|---|---|
| HER 2-neu | | |
| Negative | 114 | 82.0 |
| Positive | 25 | 18.0 |
| ER | | |
| Negative | 35 | 25.2 |
| Positive | 104 | 74.8 |
| PR | | |
| Negative | 42 | 30.2 |
| Positive | 97 | 69.8 |
| Classification | | |
| Others | 105 | 75.5 |
| Triple negative | 19 | 13.7 |
| Triple positive | 15 | 10.8 |

ER: Estrogen receptor, PR: Progesterone receptor, HER: Human epidermal growth factor.

### *Adjuvant treatment*

Among the 139 patients with MIBC, 120 (86%) patients were given chemotherapy as adjuvant according to the TNM staging and guided by the biological profile; (42.5%) 51 cases received high-risk protocol (anthracycline and taxanes) of which (13.7%) 19 patients were triple-negative breast cancer, (10.8%) 15 patients were triple-positive breast cancer and (18%) 25 cases were for being node positive while (57.5%) 69 cases received anthracyclines only and 13.7% representing 19 cases who did not receive any chemotherapy. Adjuvant endocrine treatment was given to 116 patients (83.5%); in combination with chemotherapy in 98 patients (84.5%) and alone in 18 patients (15.5%). Targeted therapy was given to 21 patients (15%).

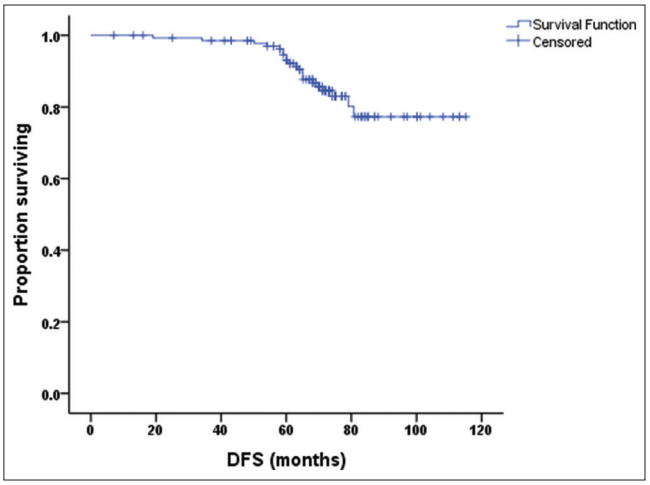


*Figure 1: Disease-free survival of microinvasive breast cancer patients*

### *Relationships between tumor characteristics and clinical outcome*

Clinical follow-up information was available for all patients. Median follow-up time was 72.1 months and ranged from 7.0 to 115.2 months (Figures 1-5) and all patients by the end of the study were alive. Breast-related positive events, such as local recurrence or distant metastases, occurred in 21 patients (15%); 8 patients (38.1%) after BCS and 13 patients (61.9%) after mastectomy (Table 3).

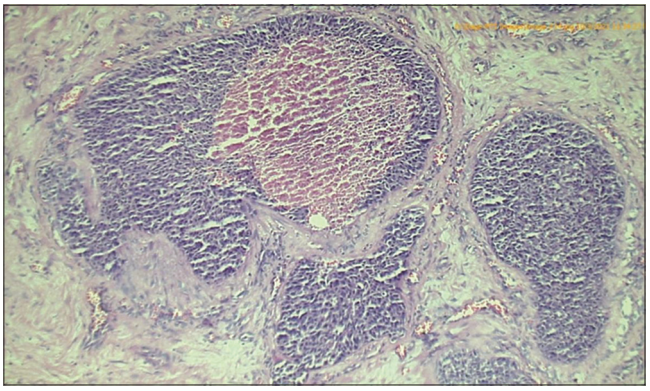

*Figure 2: A case of comedo-ductal carcinoma in situ with microinvasion into surrounding stroma (H and E stain ×100)*

DFS was 100% for those who received hormonal, 95% for those who received chemotherapy only, 92.1% for those who received high-risk protocol chemotherapy with hormonal treatment, and 96.9% for those who received chemotherapy less than or equal to four cycles with hormonal treatment. Tables 4-7 show DFS in relation to different patients' characteristics.

## Discussion

A palpable mass was the main symptom of MIBC lesions [19], [20]. In addition, nipple discharge was commonly encountered in MIBC. Factors including age, menopausal status, and family and personal history of breast cancer were not significantly affecting DFS, which were consistent with a study by Ozkan-Gurdal *et al*. [21].

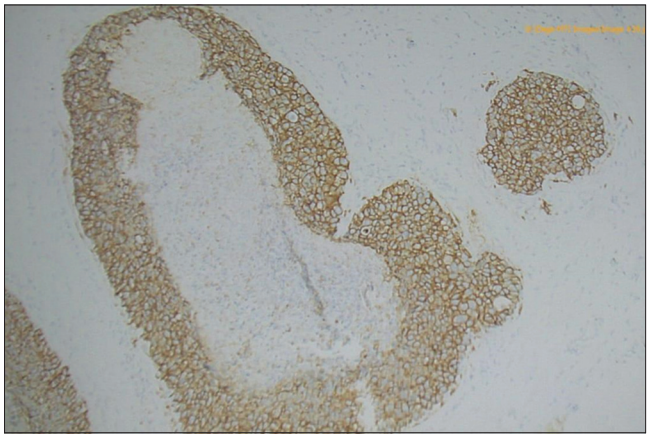

*Figure 3: A case of microinvasive duct carcinoma expressing human epidermal growth factor receptor 2-neu (+ve score 3) in both in situ comedo and invasive components (DAB ×100)*

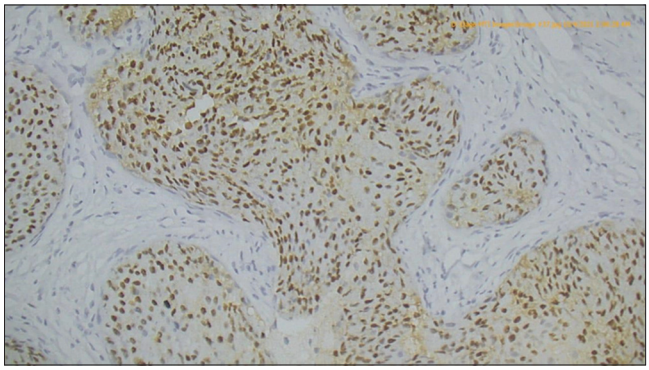

*Figure 4: A case of microinvasive duct carcinoma showing marked estrogen receptor-positive reaction in both in situ and invasive components (DAB ×100)*

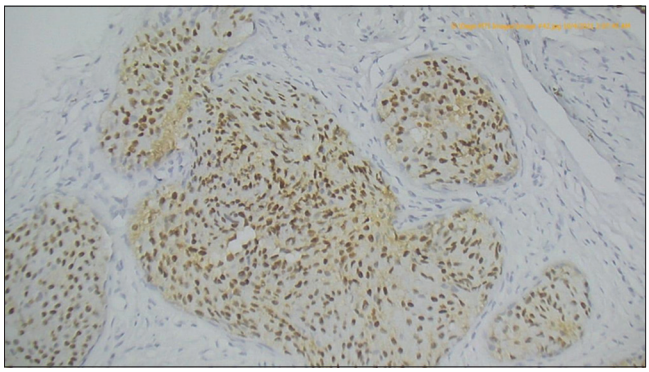

*Figure 5: A case expressing high progesterone receptor positivity in situ ductal carcinoma in situ and in the surrounding invasive clusters (DAB ×100)*

**Table 3: Distribution of recurrent cases among operation types (n = 139)**

| Operation | Recurrence | |
|---|---|---|
| | No | Yes |
| | n (%) | n (%) |
| BCS | 46 (39.0) | 8 (38.1) |
| MRM | 72 (61.0) | 13 (61.9) |
| Total | 118 (100) | 21 (100) |

BCS: Breast conservation surgery, MRM: Modified radical mastectomy.

**Table 4: DFS in relation to personal characteristics (n = 139)**

| Characteristics | n | No. of events | DFS (%)* | |
|---|---|---|---|---|
| | | | 5 years | p-value |
| All | 139 | 21 | 94.6 | |
| Age | | | | |
| ≤45 years old | 52 | 7 | 91.7 | 0.631 |
| >45 years old | 87 | 14 | 96.3 | |
| Family history | | | | |
| Negative | 118 | 20 | 93.7 | 0.281 |
| Positive | 21 | 1 | 100.0 | |
| Menopausal status (n = 130)** | | | | |
| Premenopausal | 69 | 11 | 92.4 | 0.810 |
| Postmenopausal | 61 | 8 | 96.4 | |
| Residence | | | | |
| Cairo Metropolitan Area | 95 | 13 | 95.6 | 0.181 |
| Others | 44 | 8 | 92.1 | |
| Hypertension | | | | |
| No | 113 | 19 | 94.3 | 0.281 |
| Yes | 26 | 2 | 96.0 | |
| Diabetes | | | | |
| No | 116 | 20 | 93.6 | 0.191 |
| Yes | 23 | 1 | 100.0 | |
| Performance status | | | | |
| 1 | 115 | 19 | 93.5 | 0.413 |
| 2 or more | 24 | 2 | 100.0 | |

*Median not reached, **patients with perimenopausal status were excluded, DFS: Disease-free survival.

Pathologically, MIBC tended to be of T2 (73%), Grade 2 (94%), and of ductal carcinoma type (93.5%) which was similar to the results of the previous studies [22], [23], [24].

### *ER PR*

Approximately 50–75% of DCIS were ER and/or PR-positive tumors, and reported expression rates of ER and/or PR in microinvasive carcinoma ranged from 50% to 68% [19], [20], [21], [22], similar to the findings in our study. ER (-)/PR (-) patients with MIBC had poorer prognosis compared with patients with MIBC who were either ER (+) and/or PR (+). This characteristic was primarily due to the fact that patients of MIBC with ER (+) and/or PR (+) were provided with adjuvant endocrinal therapy. By contrast, ER (-)/PR (-) patients with MIBC were not administered endocrine treatment, indicating the efficiency of endocrinal therapy.

**Table 5: DFS in relation to clinicopathologic characteristics (n = 139)**

| Characteristics | n | DFS (%)* | | |
|---|---|---|---|---|
| | | No. of events | 5 years | p-value |
| Presenting symptoms | | | | |
| Mass | 129 | 20 | 95 | 0.526 |
| Others | 10 | 1 | 90 | |
| Laterality (n = 138)** | | | | |
| Left | 69 | 7 | 96.8 | 0.096 |
| Right | 69 | 14 | 92.3 | |
| Diagnosis | | | | |
| Invasive duct carcinoma | 129 | 19 | 95.1 | 0.52 |
| Others | 10 | 2 | 88.9 | |
| Tumor size | | | | |
| T1+Tis | 26 | 2 | 91.6 | 0.559 |
| T2 | 102 | 17 | 95.8 | |
| >T2 | 11 | 2 | 90.9 | |
| LN status | | | | |
| N0 | 114 | 16 | 94.3 | 0.378 |
| N1 | 16 | 2 | 100 | |
| N2 and N3 | 9 | 3 | 87.5 | |
| Category | | | | |
| CIS | 30 | 5 | 100 | 0.727 |
| Other than that | 109 | 16 | 93.2 | |
| Stage (n=138)*** | | | | |
| Stage I | 20 | 2 | 88.7 | 0.702 |
| More than Stage I | 118 | 18 | 95.5 | |
| Grade | | | | |
| ≤Grade 2 | 133 | 21 | 94.4 | - |
| Grade 3 | 6 | 0 | 100 | |
| Hormone receptor status | | | | |
| Negative | 24 | 2 | 95.5 | 0.33 |
| Positive | 115 | 19 | 94.5 | |
| HER2-neu status | | | | |
| Negative | 114 | 16 | 94.4 | 0.551 |
| Positive | 25 | 5 | 95.7 | |

*Median not reached, ** a case with bilateral breast cancer was excluded, *** a case with Stage 0 was excluded, no test is computed because all cases in one group are censored, DFS: Disease-free survival, CIS: Carcinoma *in situ*, HER: Human epidermal growth factor, LN: Lymph node.

### *HER 2-neu*

It is well known that HER 2 (+ve) breast cancer is associated with a poor prognosis, even at the pT1a stage [23], [24]. However, the clinical significance of HER 2 positivity in MIBC has rarely been studied and remains controversial [25], [26]. Our findings demonstrated that HER2 positivity was associated with high-grade pathologic features; extensive high-grade DCIS with comedo necrosis and these aggressive features are commonly associated with HER 2 overexpression [27], [28]. In some studies, HER 2 overexpression in DCIS has been suggested as a predictor of rapid progression to invasive carcinoma [29], [30].

**Table 6: DFS in relation to tumor biomarker (n = 139)**

| Characteristics | n | n of events | DFS (%) | p-value |
|---|---|---|---|---|
| | | | 5 years | |
| Classification | | | | |
| Triple positive | 15 | 5 | 92.9 | 0.166 |
| Triple negative | 19 | 2 | 94.1 | |
| Others | 105 | 14 | 94.9 | |
| ER status | | | | |
| Negative | 35 | 3 | 93.7 | 0.207 |
| Positive | 104 | 18 | 94.9 | |
| PR status | | | | |
| Negative | 42 | 8 | 92.1 | 0.359 |
| Positive | 97 | 13 | 95.7 | |

DFS: Disease-free survival, ER: Estrogen receptor, PR: Progesterone receptor.

HER 2 positivity does not appear to be associated with significant axillary nodal metastasis, disease recurrence, or disease progression in our study population. These results are in agreement with earlier studies, Kapoor *et al*. [31]. However, the clinical outcome and treatment strategy for HER 2 (+ve) MIBC were not significantly different from those of the HER

**Table 7: DFS in relation to treatment characteristics (n = 139)**

| Characteristics | n | DFS (%)* | | |
|---|---|---|---|---|
| | | No. of events | 5 years | p-value |
| Operation | | | | |
| BCS | 54 | 8 | 88.1 | 0.878 |
| MRM | 85 | 13 | 98.8 | |
| Chemotherapy | | | | |
| Yes | 120 | 21 | 93.9 | - |
| No | 19 | 0 | 100.0 | |
| Treatment regimen (n = 120)** | | | | |
| Anthracycline and taxanes | 51 | 8 | 93.7 | 0.491 |
| Anthracycline-containing regimen | 69 | 13 | 94.1 | |
| Number of cycles** | | | | |
| ≤4 | 37 | 6 | 94.6 | 0.998 |
| 5 and 6 | 48 | 9 | 95.7 | |
| 7–9 | 35 | 6 | 90.5 | |
| RT | | | | |
| Negative | 62 | 9 | 100.0 | 0.738 |
| Positive | 77 | 12 | 89.9 | |
| Hormonal therapy | | | | |
| No | 23 | 2 | 95.2 | 0.395 |
| Yes | 116 | 19 | 94.5 | |

*Median not reached, **patients who did not receive chemotherapy were excluded, no test is computed because all cases in one group are censored, BCS: Breast conservation surgery, MRM: Modified radical mastectomy, DFS: Disease-free survival, RT: Radiotherapy.

2(−ve) MIBC cases. Microinvasive breast carcinoma has excellent prognosis, regardless of HER2 status [31]. Similar to what we discovered in our study, Margalit *et al*. demonstrated that ER/HER2 status was not significantly associated with recurrence in MIBC [32]. Although MIBC was not a predictor of recurrence, multivariate analysis found higher rates of recurrence for HER2-positive and hormone receptor-negative tumors [33].

As previous studies dealing with MIBC triple-negative and HER2-positive tumors are both known to be aggressive phenotypes, their underlying and differing roles in cancer progression need more advanced research.

### *LN metastasis*

Axillary LNs metastasis may represent the ability of invasion of cancer and contributed to the shortened DFS [34]. Our rate of axillary metastases at diagnosis was 18%. This is higher than the 6–11% rate of axillary metastases reported in other studies of MIBC [35]. This higher rate may be attributable to enhanced detection of minimal regions of microinvasion and dedicated breast pathology review.

The necessity of performing SLN biopsy in cases with MIBC is not well established. Although in 2005, the American Society of Clinical Oncology did not find enough evidence to recommend performing SLN biopsy in patients with MIBC and SLNB may not be useful in MIBC due to the low risk of LN metastasis and good prognosis [36].

However, several other studies recommended performing such biopsies because of the reported high incidence of micrometastatic breast carcinoma in SLN and the debated clinical implications, as well as the significant chance of microinvasive tumor being upstaged to invasive tumor following full histopathologic evaluation [37]. Only 46 MIBC cases in our study had SLN biopsy, as the decision to perform a SLN dissection or axillary LN dissection was the decision of the surgeon, with 10 cases (22%) of them which were positive for tumor cells and proceed to axillary dissection.

### *Surgery*

The increased incidence of MIBC over the past decade is likely attributable to increased sensitivity of breast imaging over time. Equivalence of BCS and mastectomy suggests that these additional tumor foci are not clinically significant when appropriate adjuvant therapies are administered [38]. Improvements in systemic therapies and RT techniques in recent years have relevance to management of MIBC with BCS [39].

The authors concluded that there was no independent impact of multifocal or multicentric tumors on local recurrence and BCS is a safe surgical option [40]. No significant difference in rates of local or distant recurrence according to the type of surgery, either BCS or mastectomy in our study as in several nonrandomized studies has investigated the impact of MIBC on recurrence and breast cancer-specific survival in relation to type of surgery (BCS vs. mastectomy) [41], [42].

As previous studies dealing with MIBC triple-negative and HER2-positive tumors are both known to be aggressive phenotypes, their underlying and differing roles in cancer progression need more advanced research. In comparison to those treated with mastectomy, it has been suggested that it is the RT of all BCS patients that describe the variations found [43] but this is strongly denied by Prior Danish trials found a higher recurrence and death incidence in recent patients and a poorer post-BCS result than mastectomy [41].

### *Chemotherapy*

Recommending treatment for patients with MIBC who had insufficient information caused by small sample size and varying definitions is quite difficult. Adjuvant chemotherapy plays a very important role in breast cancer treatment, especially for triple-negative breast cancer [44], [45]. However, risk–benefit balance of chemotherapy should be considered to avoid widespread use of aggressive treatments for patients with MIBC.

To our knowledge, only a few studies have provided information on adjuvant treatment received by patients with MIBC. Our study is unique since we were the first to select patients with MIBC to review the necessity of adjuvant chemotherapy after surgical operation. We found no much statistical significance on the 5-year DFS where hormonal treatment was superior to those who received chemotherapy alone or chemotherapy together with hormonal treatment. This result indicates that chemotherapy may have short-term benefits for patients with MIBC. However, long-term chemotherapy may produce side effect on patients with MIBC caused by adverse events. Therefore, selecting the best implication of adjuvant chemotherapy for MIBC is important. According to our subgroup analysis, ER (-)/PR (-) patients had the best implication.

Thus, adjuvant chemotherapy should be cautiously administered to patients with MIBC. Adjuvant chemotherapy can be considered to patients with negative hormonal receptors when costs and benefits of adjuvant chemotherapy are weighed accurately. These patients have substantial risk of relapse within the first 5 years after surgical operation. In other words, the definition by Schwartz, which is beyond the definition by the seventh edition of the AJCC staging manual, should include part of invasive ductal carcinoma classified as pT1a or pT1b according to TNM staging in the seventh edition of AJCC Staging Manual published in 2010 [46].

However, our study has limitations. We cannot establish firm conclusions because of the small sample size and short follow-up period.

## Conclusion

An increased incidence of MIBC is attributable to widespread usage of MRI and introduction of breast cancer screening programs. Despite limitations of published studies to date on multifocal and multicentric cancers treated with BCS, rates of local recurrence are low and there is no clear evidence for any survival detriment. This has permitted an element of surgical equipoise and prompted the first randomized controlled trial of oncoplastic surgery for MIBC. Surgery must achieve negative resection margins for each tumor with acceptable cosmetic results.

Careful evaluation of "double boosts" is essential with documentation of acute and chronic RT effects. The adoption of breast cancer surgical procedures is based on the multidisciplinary consults and the availability of treatment resources. With the emerging early detection strategies and oncoplastic procedures, more conservative approaches are propagated and encouraged in developing countries.

Patients with MIBC have the good prognosis. However, patients who are negative hormonal receptors have relatively substantial risk of relapse within the first 5 years after surgical operation. Adjuvant chemotherapy can only improve the outcomes of patients with negative hormonal receptors. Further studies with prolonged follow-up of large cohort are warranted to assess the prognostic significance and treatment of this lesion.

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