Microinvasive breast cancer and the role of sentinel lymph node biopsy

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Research Article

Keywords: Sentinel lymph node biopsy, Microinvasive breast cancer, long term follow up

Posted Date: October 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-966472/v1

Abstract

Whether sentinel lymph node biopsy (SLNB) should be performed in patients with microinvasive breast cancer (MIBC) has been a matter of debate over the last decade. MIBC has a favorable prognosis. Metastasis to the axilla is rare in MIBC, but such axillary mets would impact on treatment recommendations. In this study, we evaluated clinical and histological features in both MIBC and background DCIS including the ER, PR, and HER-2/neu, number of foci of MIBC, and the extent of the DCIS, nuclear grade, presence of comedo necrosis, as well as surgical procedures, adjuvant treatment and follow up, to identify variables which predict disease free survival (DFS), as well as the factors which influence clinical decision making. In the group of 72 patients with MIBC, an average mean patient follow-up time was 32 months. Three patients with MIBC had recurrence, and two deceased, leaving 5 patients in total with poor long-term outcomes and a DFS rate of 91.7%. Performing mastectomy, high nuclear grade, and negativity for ER and HER-2 were found to be associated with the use of SLNB, although none of these variables were found to be associated with DFS. One positive lymph node case was discovered following SLNB in our study. This suggests the use of SLNB may provide diagnostic information to some patients, although these are the anomalies. When comparing patients who had undergone SLNB vs those that had not, there was no difference in DFS; while following multivariate analysis, patients who underwent adjuvant radiation (HR: 0.093, P = 0.04)) were found to have improved DFS. Certainly, the use of SLNB in MIBC is quite the conundrum. It is important to acknowledge that surgical complications have been reported, and traditional metrics used for risk assessment in invasive breast cancer may not necessarily represent risk in the setting of microinvasion.

Introduction

Microinvasive in breast cancer is defined as invasion of less than 1mm into adjacent stroma [1]. Prior to this there was discrepant reporting of MIBC, with different definitions of microinvasion [1–6], resulting in significant controversy. MIBC arises in the setting of DCIS and generally, patients diagnosed with DCIS have a normal life expectancy and a long-term survival of around 98% after 10 years [7, 8]. Like DCIS, MIBC has been reported to be associated with good overall clinical outcomes. For example, Kwon et al. showed the 5-year recurrence free survival to be 97.2 %, although after 10 years of follow up Parikh et al. showed a 10-year rate of recurrence free survival to be 90.7 % [9, 10]. Most recently, based on the records review of 525,395 women, Sopik et al. demonstrated 20-year breast cancer-specific mortality to be 3.8% for pure DCIS, and 6.9% for MIBC, with an adjusted hazard ratio for death associated with MIBC when compared to pure DCIS to be 2.00 (95% CI 1.76–2.26; $p < 0.0001$) [11].

Compared to DCIS, MIBC is seen in association with high nuclear grades, necrosis, human epidermal growth factor receptor 2 (HER2) positivity and a high Ki-67 positivity index, whereas the rates of estrogen receptor (ER) and progesterone receptor (PR) positivity are lower in patients with microinvasive carcinoma arising the background of extensive DCIS [12]. For the purposes of treatment decision making, validating the reproducibility for different methods of risk stratification in MIBC will be important. The role of sentinel lymph node biopsy (SLNB) in MIBC is currently not well defined, while the rate of axillary metastases has been observed to be very low (0–11 %) [10, 13]. In a large study of 2609 patients with MIBC who underwent SLNB, only 76 (2.9%) patients were found to have sentinel lymph node metastases [14].

Therapeutic approaches can result in overtreatment of some patients with breast cancer. The Marmot Report published in 2012 acknowledge the negative effects of overtreatment to women's health[15]. There are many considerations for surgical interventions: poor cosmesis after surgery, chronic pain due to sentinel lymph node biopsy procedure in the axilla, and the possibility of no long-term outcome difference following the biopsy procedure [13]. ER, PR, HER's-2/neu statuses have been extensively studied in invasive breast cancer, while less data is available regarding ER, PR and HER-2 in MIBC [6, 16, 17]. Although highly prevalent, there is little direct evidence that hormonal status is to be associated with improved long term outcomes in MIBC[18]. It is generally accepted that hormone receptor (HR) positive patients receive benefit from adjuvant endocrine therapy, however adjuvant chemotherapy in MIBC has been found to only improve the outcomes of ER(-)/PR(-) patients which did not overexpress Ki-67 [19].

Performing a risk assessment is important for guiding treatments and for MIBC there is limited information. The present study aims to evaluate the clinical and histological characteristics of both MIBC and DCIS including ER, PR, and HER-2/neu status, number of foci of MIBC, the size extent of the background DCIS and nuclear grade, presence of comedo-necrosis, as well as

surgical procedures, adjuvant treatment and clinical follow-ups, to identify variables which predict disease free survival, as well as the factors which influence clinical decision making.

Materials And Methods

Case selection

Upon Institutional review board (IRB) approval (Lifespan IRB: 751551-10), a retrospective natural language search of the pathology database (Cerner CoPath) for patients over the age 18 years was performed from July 2010 to May 2020. Cases with a diagnosis of “microinvasive breast cancer” were retrieved. Cases with definitively invasive carcinoma (>1mm) were excluded. Mammography was the single most common approach to breast cancer detection in this cohort of patients and all current AJCC protocols were followed in order to ensure the most current recommendations for the diagnosis of microinvasion (1mm). Follow up data for death and recurrence was provided by the cancer registry at the Lifespan Health System.

Pathology examination

All cases were reviewed by two breast pathologists. Each focus of microinvasion was measured individually, with multiple foci not being added together. Figure 1 demonstrates histological findings in MIBC, including findings seen during immunostaining. We chose a 2mm cutoff for close margins are this has been used by other groups. The extent of DCIS was estimated by sequential sectioning of the slices or calculated from the ratio of number of blocks with DCIS to total slides or by estimating the number of centimeters of DCIS disease present comprising the number of blocks of DCIS multiplied by 0.4 cm in non-sequential setting [20].

Immunohistochemistry

Anti-estrogen receptor (ER; 1:50; Dako, Santa Clara, CA; clone 1D5), progesterone receptor (PR; 1:400; Dako; clone 1A6), HER2/ neu (Dako HercepTest), anti-p63 (1:100; Biocare; clone 4A4), anti- calponin (1:500; Dako; clone CALP), and anti-smooth muscle heavy chain (1:100, Cell Marque; clone CMC569) were used for immunohistochemistry. Immunoreactivity was detected using the Dako EnVision method according to the manufacturer’s recommended protocol. Immunohistochemistry for ER and HER-2/neu was scored according to expression guidelines published by updated College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO)[21], which was recently updated in 2018[22]. ER and PR wwere reported as positive when greater than 1% of tumor nuclei showed staining and negative when less than 1% of tumor nuclei showed staining, HER-2/neu was reported as negative if scored as 1+ and positive when scored as 3+. Tumors scored as 2+ underwent confirmatory testing with chromogenic in situ hybridization (CISH).

Chromogenic in situ hybridization

Her-2/neu CISH was performed by a VENTANA 4B5 Inform HER2 dual-color on the BenchMark Ultra system (INFORM HER2 DNA dualcolor assay—Roche Tissue Diagnostics, VENTANA Medical Systems, SA) per the manufacturer-dictated protocol. Invasive breast cancer and synchronous DCIS components were scored and recorded separately according to the updated ASCO/CAP guidelines[22]: a *HER2* copy number of 6.0 or higher per cell or a *HER2*:CEP17 ratio of 2 or higher was considered to represent HER2 amplification. *HER2* copy numbers of <4 signals per cell and *HER2*/CEP17 ratios of <2 was nonamplified.

Statistical analysis

The Fishers exact test was used to determine differences in proportions and t tests were used to compare differences in means for parameters including patient age, surgery type, radiation status, DCIS size, DCIS nuclear grade, pathologic necrosis, ER status, PR status and HER-2 status. Kaplan-Meier survival analysis was used to evaluate disease free survival (DFS) rate as a function of time, while the log-rank method was used to compare differences between groups. Univariate and multivariate analyses of DFS were performed by Cox proportional-hazard regression. All tests were 2-sided, with P values < .05 considered statistically significant. All analyses were performed using SPSS statistics version 23.0.0.3.

Results

The patient characteristics and pathology findings are summarized in Table 1. The mean age of our cohort was 56.65 years. Of the 72 cases of MIBC, 50 patients received breast-conserving therapy (BCT; lumpectomy), and 22 underwent mastectomy (MST). 43 patients underwent SLNB, while 29 did not. Sentinel lymph node metastases were identified in 2 patients, 1 had a macro metastasis (> 2mm), and 1 had isolated tumor cells (defined as <0.2 mm with <200 cells). Due to the low nodal positivity rate, there were no significant associations for SLNB positivity between patient's age, SLNB status, surgical procedure, radiation status, DCIS size, MIBC foci, margin status, nuclear grade, histologic necrosis, as well as ER, PR, and HER-2/neu status. Following surgery, 45 of the 72 patients received adjuvant radiation therapy (RT), while 27 patients did not.

Broadly, patients were placed into the following RT patient groups by surgical status: BCT with whole breast RT (37); BCT with partial breast RT (2); BCT with NOS RT (5); BCT without RT (6); MST with post mastectomy RT (1); MST without RT (21). And into the following RT patient groups by SLNB status: SLNB (-) with whole breast RT (21); SLNB (-) with partial breast RT (1); SLNB (-) with NOS RT (1); SLNB (-) without RT (6); SLNB (+) with whole breast RT (17); SLNB (+) with partial breast RT (1); SLNB (+) with NOS RT (4); SLNB (+) without RT (21).

The mean DCIS size was 3.1cm and nuclear grading was as followed: grade 1 (7), grade 2 (21), grade 3 (44). 56 of the DCIS cases had necrosis, while 16 did not. ER, PR, and HER-2 were tested for concordant positivity in both the MIBC and DCIS components. ER was positive in 46 patients and negative in 16 patients. PR was positive in 25 patients and negative in 23. HER-2/neu was positive in 20 patients and negative in 28 patients.

Clinicopathological features

Many features were found to be associated with treatment/management decisions and long-term outcomes. First, SLNB was more common in patients in younger patients (P= 0.001) and in those who underwent mastectomy (P=0.004), and RT (P=0.025). SLNB was also more commonly used in larger DCIS size (P=0.012), DCIS with high nuclear grade (P=0.023), and in patients who were ER (P=0.044) and PR (P=0.048) positive. The use of BCT was more commonly followed with adjuvant RT when compared to patients which had mastectomy (P=0.001) and with a larger DCIS size (P=0.001). RT was found to be associated with less extensive DCIS (P=0.014). The remaining clinicopathological features were not statistically significant.

Disease free survival

DFS was defined as by the presence of recurrence or death. The average mean patient follow-up time was 32 months. Three patients with MIBC had recurrence and two deceased, leaving 5 patients in total with poor DFS and a DFS rate of 91.7%. The characteristics for these patients are presented in Table 2.

Table 2
Characteristics of patients with poor long-term outcomes. SLNB, Sentinel Lymph Node Biopsy; DCIS, Ductal Carcinoma in Situ; MIBC, Microinvasive Breast Cancer.

Patient	Age	SLNB	DCIS size (mm)	MIBC foci	Margin status	Nuclear grade	Necrosis	ER	PR	HER-2	Treatment	Outcome
1	68	Yes	18	1	Close	3	Present	Neg	Neg	Pos	BCT, RT(+)	Death
2	40	Yes	40	1	Neg	3	Present	Pos	-	-	MST, RT(-)	Recurrence
3	78	No	50	1	Neg	3	Present	Pos	-	-	MST, RT(-)	Death
4	98	No	68	3	Pos	2	Present	Pos	Neg	Neg	BCT, RT(-)	Recurrence
5	52	Yes	24	1	Close	3	Present	Pos	Pos	Neg	BCT, RT(-)	Recurrence

None of the following variables were significant following univariate cox regression: age, SLNB, surgery, radiation status, DCIS size, nuclear grade, necrosis, ER, PR and HER-2 status. Following multivariate analysis, positive adjuvant radiation status (HR: 0.093 (0.01-0.901), P value = 0.04) was found to predict DFS. Results for Cox-regression can be found in Table 3. Survival curves were also calculated using the Kaplan Meier, log rank method. None of the variables were found to be associated with DFS (P>0.05).

Table 3
Univariate and multivariate analyses of long-term outcomes using the Cox Proportional-Hazard Regression. HR, Hazard Ratio; SLNB, Sentinel Lymph Node Biopsy; DCIS, Ductal Carcinoma in Situ. Significant features (P≤0.05) are shown in bold.

	Univariate HR	Confidence Interval	P Value	Multivariate HR	Confidence Interval	P Value
Age (years)	0.513	0.0507-4.608	0.551	1.070	0.998-1.146	0.051
SLNB	1.334	0.242-7.349	0.741	1.750	0.285-10.76	0.546
Surgery	0.639	0.099-4.114	0.638	0.182	0.019-1.771	0.142
Radiation status	0.183	0.02-1.609	0.126	**0.093**	**0.01-0.901**	**0.040**
DCIS size	1.451	0.263-7.996	0.669	0.601	0.059-6.076	0.601
MIBC foci	0.808	0.383-1.704	0.576	0.835	0.466-1.498	0.546
Margin status	1.151	0.493-2.689	0.748	2.062	0.575-7.395	0.267
Nuclear grade	2.774	0.394-19.534	0.306	4.295	0.537-34.386	0.170
Necrosis	3.814	0.004-24.554	0.444	3.103	0.05-20.694	0.448
ER status	1.468	0.268-8.054	0.658	2.246	0.411-12.27	0.350
PR status	0.234	0.024-2.252	0.209	0.243	0.022-2.732	0.243
HER-2 status	1.523	0.214-10.828	0.674	0.931	0.114-7.598	0.946

Discussion

The present work evaluated clinical parameters including SLNB, surgical type, radiation status, and long-term outcomes in relation to histological features in MIBC and associated DCIS. Overall, MIBC was found to have a favorable prognosis and only 6/78 (7.7%) patients were found to have poor DFS, congruent with other studies which have shown recurrence free survival rates between 90-97%[6, 9, 10, 23]. These studies had an average follow up time of 64.9 months, an overview of all MIBC publications based on the 1mm AJCC cutoff is summarized in Table 4.

Table 4
Significant literature based on the 1mm AJCC categorization of MIBC. AJCC, American Joint Committee on Cancer; SLNB, Sentinel Lymph Node Biopsy; BCT, Breast Conservative Therapy; RT, Radiation Therapy; DFS, Disease Free Survival; RFS, Recurrence Free Survival; OS, Overall Survival.

Study	Institution	Years	Case number	SLNB (%)	BCT (%)	RT (%)	Follow up (months)	Survival
Present study	Brown	2002-2021	72	43 (60%)	50 (69%)	45 (63%)	32 (median)	DFS % 91.7
Zhang, 2021[16]	University of Rochester	2007-2019	46	33 (72%)	21 (46%)	15 (33%)	38 (median)	RFS 100%
Si/2020[26]	Jiaxing University	2006-2015	359	242 (67%)	26 (7%)	17 (5%)	61 (median)	OS 99.36%
Zhang, 2020[31]	Hebei Medical University	2011-2018	264	164 (62%)	23 (9%)	19 (72%)	47 (median)	RFS 95.4%
Kim, 2018[12]	Seoul National University	2003-2014	136	110 (81%)	55 (40%)	-	48 (median)	RFS 97.8%
Pu, 2018[32]	Sichuan University	1997-2014	242	-	26 (11%)	23 (9%)	109 (median)	DFS 96.89%
Li, 2015[33]	Tianjin Medical University	2003-2009	93	2 (2%)	1 (1%)	-	100 (median)	RFS 90.9%
Wang, 2015[17]	Tianjin Medical University	2002-2009	131	-	-	-	69 (median)	DFS 95.2%
Matsen, 2014[27]	Memorial Sloan Kettering Cancer Center	1997-2010	414	414 (100%)	198 (48%)	174 (42%)	59 (median)	RFS 95.9%
Shatat, 2013[34]	University of Kansas	1998-2012	40	-	19 (48%)	-	30 (mean)	OS 100%
Kapoor, 2013[35]	John Wayne Cancer Institute	1995-2010	45	31 (69%)	24 (53%)	-	83 (median)	RFS 93.7%
Margalit, 2012[6]	Harvard	1997–2005	83	53 (64%)	52 (63%)	53 (64%)	77 (median)	RFS 94.7%
Lyons, 2012[36]	Memorial Sloan Kettering cancer center	1996-2004	112	111 (100%)	60 (53%)	51 (46%)	72 (median)	DFS 91%
Pimiento, 2011[37]	H.Lee Moffitt cancer center	1996-2009	87	87 (100%)	59 (68%)	0 (0%)	74 (median)	OS 94.2%
Parikh, 2010[10]	Yale	1973–2004	72	4 (6%)	72 (100%)	72 (100%)	107 (median)	RFS 90.7%
Vieira, 2010[22]	New York University	1993–2006	21	14 (67%)	(55%)	-	36 (mean)	OS 100%
Kwon, 2010[9]	Seoul National University	2000-2006	120	-	(53%)	30 (25%)	61 (median)	RFS 97.2%

In the present study, the use of SLNB was more often confined to patients undergoing mastectomy and was also performed more commonly in background DCIS Showing high nuclear grades with negative ER and positive HER-2 receptor status. Only 1/44 patients had positive lymph nodal metastasis (>0.2mm) following S:NB and no variable was able to statistically predict nodal positivity. A finding possibly secondary to the low propensity of lymph node metastasis in MIBC. Importantly, when comparing patients who had undergone S:NB, vs those that had not, there was no difference in long term outcome in our study. Positive adjuvant radiation status (HR: 0.093 (0.01-0.901), P value = 0.04) was predictive of good outcomes, whereas 4/5 patients with poor DFS outcomes did not receive radiotherapy.

Despite the lack of differences in long term outcome from SLNB, surgical complications associated with SLNB biopsy have been reported. In a large study of 5327 patients performed by Wilke et al.[24], complications included axillary wound infection (1.0%), axillary seroma (7.1%), and axillary hematoma (1.4%). For older patients, SLNB was also found to be associated with an increased incidence of axillary seroma.

Moreover, we observed HER2 positivity to be relatively common in MIBC, and when compared with pure DCIS, numerous studies have reported a higher rate of HER2 overexpression in microinvasive carcinoma than in both invasive carcinomas and DCIS[6, 12]. This is counter intuitive, as HER-2 amplification has been traditionally seen to occur more often in DCIS than in invasive carcinoma[25]. Zhang et al.[16] demonstrated HER2 positivity to be associated with high-grade morphologic features, but not nodal metastasis or worse outcomes. We also did not find HER-2/neu overexpression to be associated with recurrence in those MIBCs although in invasive breast carcinomas, HER-2/neu oncogene has been demonstrated to be a an independent prognostic indicator in cancers that are at high risk of early recurrence[26]. These findings could be secondary to the good overall outcomes in MIBC, as well as the small patient population seen in our study. Nonetheless, evaluating the role of HER2-targeted therapy will need to be validated in clinical setting by future studies.

In the present study, although we analyzed additional clinicopathological parameters such as the number of microinvasive foci, the extent and histology of the background DCIS, none of these were found to be associated with long term outcomes. Although some studies have found patients with multiple foci of microinvasive had worse disease-free survival outcomes [27], a large study (414 patients) by Matsen et al.[28] showed that there was no higher risk of nodal involvement for patients with ≥2 foci of microinvasion when compared to 1 focus.

The recent knowledge in tumor microenvironment also gives us new insight that the number of microinvasive foci may be less important than the stroma itself and the overall tumoral microenvironment. Computationally[29], predictors of breast cancer outcomes have been found to arise from stromal rather than tumors cells. While digital image analysis has found the formation of stroma in triple negative biomarker cancer to be associated with a poor prognosis, high stroma has been shown to be associated with favorable prognostic outcomes in luminal tumors[30]. Histologically, Zhai et al.[31] identified the presence of myxoid stroma to determine clinical outcomes and PD-L1 immunophenotype in patients with breast cancer, suggesting that routine assessment could be used to identify clinical risk and better tailor the need for SLNB and therapeutic management in MIBC as well.

There were several pitfalls to the present study. Firstly, this was a retrospective study which always carries the risk of selection bias. Secondly, we did not perform molecular testing and thirdly, due to the low incidence of MIBC, we were unable to increase our cohort size any further. With this being said, multi-institution collaboration will be important for future studies.

In summary, when comparing patients who had undergone SLNB to those that had not, there was no different in long term outcomes. The decision to undergo SLNB in MIBC should be made with the knowledge that surgical complications are reported, and traditional metrics for risk stratification and treatment decision making in invasive mammary carcinoma may not hold true in the setting of microinvasion.

Acknowledges

We thank Tara Szymanski from the Breast Cancer Center to assist in data collection.

Declarations

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We thank Tara Szymanski from the Breast Cancer Center to assist in data collection.

Disclosures

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures

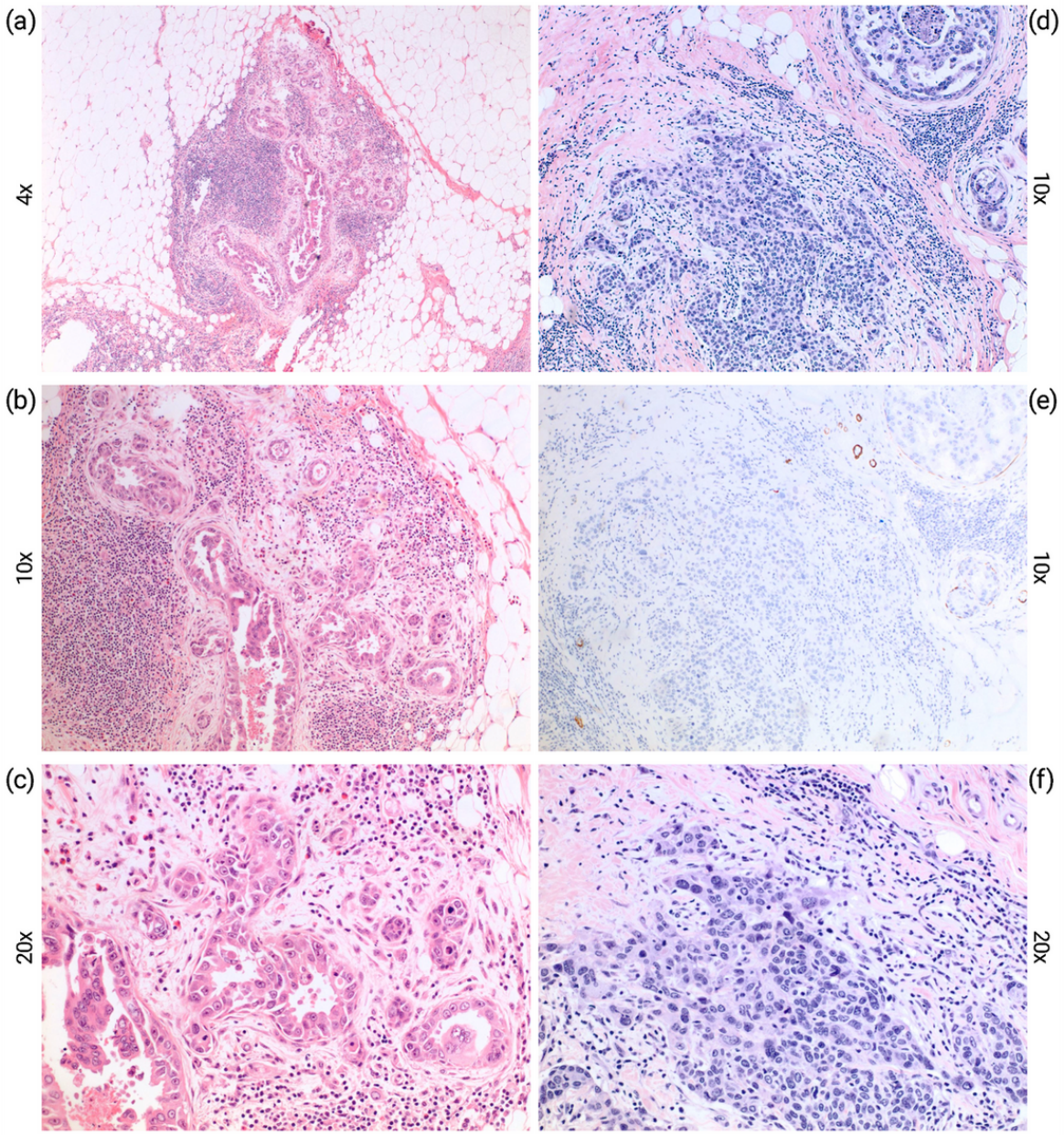

Figure 1

Representative photomicrographs from patients diagnosed with microinvasive carcinoma. a-c: Microinvasive carcinoma (0.9mm), arising in the background of ductal carcinoma in situ (DCIS) with high nuclear grade with comedo necrosis; d-f: Microinvasive carcinoma (0.8mm) arising in ductal carcinoma in situ (DCIS), solid and cribriform patterns, with comedonecrosis and associated microcalcifications. The invasive component is negative for smooth muscle myosin heavy change by immunostaining (e).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLE1.docx