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Estrogen receptor status has no prognostic relevance in metaplastic breast carcinoma

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Abstract

Background: Metaplastic breast carcinoma (MBC) is a rare histologic variant of breast cancer characterized by the presence of glandular and non-glandular components. The prognostic significance of estrogen receptor (ER) status has been scarcely studied in these tumors. We therefore investigated the prognostic relevance of ER status in MBC within our patient population.

Design: We reviewed MBC cases ($n = 125$) between January 2000 and September 2019. Histologic slides were reviewed for variables including tumor morphology and hormonal status. Additional clinical information was obtained from the electronic medical records.

Results: Of the 125 patients, 15 (12%) had ER positive tumors and 110 (88%) had ER negative tumors. Eleven (73%) ER positive tumors had ER positivity $>10\%$ and 4 (27%) had ER positivity $\leq 10\%$. ER positive tumors had a smaller median tumor size of 2.5 cm, compared with ER negative tumors with median tumor size 3.05 cm, however this difference was not statistically significant ($P = 0.82$). There were no statistical differences between ER positive and ER negative tumors in terms of histologic grade ($P = 0.34$), histologic subtype ($P = 0.65$), clinical stage

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Declaration of Competing Interest

All Authors declare that they have no conflicts of interest related to this manuscript.

Disclosures

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CRediT authorship contribution statement

Evi Abada: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Seongho Kim:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Keion Dozier:** Data curation, Visualization. **Omar Fehmi:** Data curation, Visualization. **Hyejeong Jang:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Ziad Fehmi:** Data curation, Visualization. **Sudeshna Bandyopadhyay:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

(P>0.99) or human epidermal growth factor receptor 2 (HER2) expression (P = 0.29). There was also no difference in overall survival (OS) between ER positive and ER negative metaplastic breast cancers (HR = 0.35, 95% CI, 0.003–2.67, P = 0.39).

Conclusion: Our experience suggests that ER positivity has no prognostic relevance in MBC. Regardless of ER expression status, there were no statistically significant differences in overall survival between ER positive and ER negative MBC.

Keywords

Metaplastic breast carcinoma; Breast cancer; Estrogen receptor; ER positive metaplastic breast carcinoma; Breast cancer survival; Estrogen Receptor Positive metaplastic breast cancer; Hormone receptor positive metaplastic breast cancer

Introduction

Metaplastic breast carcinoma (MBC) constitutes a rare and aggressive subtype of breast cancer which accounts for less than 5% of invasive breast cancers. [1] This malignancy is characterized by the histological presence of at least two cellular types, typically epithelial and mesenchymal components. [2] MBC was first described in 1973 by Huvos et al. and was formally recognized as a distinct pathological subtype of breast cancer in 2000. [1–3] The WHO classification of breast tumors classifies MBC as mixed metaplastic carcinoma, low-grade adenosquamous carcinoma, fibromatosis-like, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with mesenchymal differentiation. [1, 4] The majority of MBCs are triple-negative, which is defined as breast tumors that are negative for the estrogen receptor (ER), progesterone receptor (PR), and do not overexpress HER2/neu. [5] On mammography, MBCs show many similarities to invasive ductal breast cancer (IDC) as well as benign lesions, which delays and makes it difficult to make a definitive diagnosis. [6] MBCs are often larger at presentation, less likely to involve regional axillary lymph nodes, and of a higher grade than breast tumors with more common histology. [7, 8] These tumors also have a propensity to metastasize to distant sites by hematogenous rather than lymphatic spread. [9] The lack of expression of hormonal receptors (ER, PR, and HER2) in most cases of MBC has made the treatment of this disease challenging, with poor outcomes in patients. Nonetheless, the prognostic significance of ER status in MBC has been scarcely studied and may be explored for potential treatment benefits in these patients. We aimed to study the prognostic relevance of ER status in MBC, as well as its impact on overall survival (OS), defined as the time from original diagnosis to last follow up or death, within our patient population.

Materials and methods

This was a retrospective study conducted at the Department of Pathology at the Wayne State University School of Medicine/Detroit Medical Center in Michigan. Institutional review board (IRB) approval was obtained from the Wayne State University IRB (IRB-19–12–1591). We searched our institution’s database between January 2000 and April 2019 to identify patients diagnosed with MBC during this time. As previously reported, search terms used included “metaplastic breast carcinoma”, “carcinosarcoma”, “breast carcinoma

with metaplasia", "squamous cell carcinoma", "spindle cell carcinoma", "carcinoma with sarcomatoid metaplasia", "carcinoma with osseous or bony metaplasia", "carcinoma with chondroid metaplasia", and "breast carcinoma with osteoclastic giant cells." [10] We reviewed patient's demographic information, tumor characteristics (tumor size, histologic differentiation, tumor focality, histologic grade, lymphovascular invasion, lymph node metastasis, distant metastasis, estrogen receptor [ER], progesterone receptor [PR], human epidermal receptor-2[(HER-2], Ductal Carcinoma in situ [DCIS], and fibrocystic breast disease), comorbidity (obesity, smoking, history of prior cancers), treatment received, and OS. [10] Clinical tumor size was based on the largest size recorded by gross pathologic examination. ER-positive tumors were categorized as positivity $>10\%$ and positivity $\leq 10\%$ respectively. ER and PR tumor expressions were characterized using the most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. [11] HER-2 expression is as defined by the ASCO/CAP most recent update. [12] Hematoxylin and eosin-stained slides were reviewed by a surgical pathologist (EA) and a breast pathologist (SB) to confirm the diagnosis of MBC. The tumor stage is presented using the American Joint Committee on Cancer (AJCC) 8th edition staging system. [13] Histological grade was scored using the Nottingham modification of the Bloom-Richardson system based on tumor tubule formation, the number of mitotic figures in most active areas and, nuclear pleomorphism [14, 15].

Patient baseline characteristics were summarized by median (range) and frequency (percentage) for continuous and categorical variables, respectively. Group comparisons were performed by Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The distribution of OS was graphically described using Kaplan-Meier (KM) curve along with a 10-year rate and 95% confidence interval (CI). A log-rank test was used to compare KM curves between groups. Univariable and multivariable firth Cox regression models were used to assess the association between ER status (positive vs. negative) and OS in order to reduce bias in maximum likelihood estimation caused by rare events. Multivariable Cox proportional hazard regression analyses were further carried out to estimate adjusted HR by propensity score–based multivariable covariate adjustment (PSCA). The propensity score was estimated using a multivariable logistic regression model with ER status as a response variable and tumor size, histology (heterologous histology vs. others), stage (I-II vs. II-IV), metastatic disease, lymphovascular invasion, neoadjuvant therapy, hormonal treatment, progesterone receptor, chemotherapy and smoking as 10 covariates. These covariates were included in the multivariable analysis because they are known clinical confounding factors. Then both estimated propensity score and ER status were included as covariates into multivariable Cox proportional hazard models. The proportional hazard assumption was verified based on Schoenfeld residuals, and no violation was found.

Results

During the study period, a total of 135 MBC cases were identified, however, 10 cases had incomplete clinical and pathologic records and were excluded from the study. Of the remaining 125 cases, 15 (12%) had ER-positive tumors and 110 (88%) had ER-negative tumors. Of the ER-positive tumors, 11 (73%) had ER positivity $>10\%$ (Fig. 1) and 4 (27%) had ER positivity $\leq 10\%$ (Fig. 2). The median age of patients with ER-positive

tumors was 53 years (range, 33–88) and the median age of patients with ER-negative tumors was 57 years (range, 27–92) ($P = 0.27$). ER-positive tumors occurred more commonly in Black/African American (AA) women (60%), compared with Caucasian women (33%) and women from other ethnicities (7%) ($P>0.99$). ER-positive tumors also had a smaller median tumor size (2.5 cm) compared with ER-negative tumors with a median tumor size of 3.05 cm ($P = 0.82$). MBC was more likely to be a high grade (115; 92%) regardless of hormonal status ($P = 0.34$) and heterologous histology (chondroid [Fig. 3], rhabdoid [Fig. 4], osteoid [Fig. 5], osteoclastic giant cells [Fig. 6]) occurred similarly in both ER-positive and ER-negative tumors ($P = 0.65$). Other histologic patterns identified in this MBC cohort include squamous cell carcinoma [Fig. 7] and spindle cell/sarcomatous carcinoma [Fig. 8]. Patients with MBC were more likely to present with stage II disease, regardless of hormonal status ($P>0.99$). HER2 positivity was only seen in 2 (13%) patients with ER-positive tumors, compared with ER-negative tumors in which HER2 positivity was observed in 7 (6%) of the patients ($P = 0.29$). PR positivity (9; 60%) was more likely to be seen in patients with ER-positive tumors compared with patients with ER-negative tumors (8; 7%) and this difference was statistically significant ($p<0.001$). Overall, triple-negative (ER-negative, PR-negative and, HER2-negative) tumors occurred in 95 (76%) patients with MBC in this cohort. Lymph node positivity occurred in 6 (40%) patients with ER-positive tumors and 29 (26%) patients with ER-negative tumors ($P = 0.36$). Lymphovascular invasion occurred in 4 (27%) patients with ER-positive tumors and 29 (26%) patients with ER-negative tumors ($P>0.99$). There was no difference between ER-positive and ER-negative tumors in terms of disease focality ($P = 0.72$), coexistent DCIS ($P = 0.57$), fibrocystic breast disease ($P = 0.14$), being overweight or obese ($P>0.99$), smoking status ($P = 0.09$) and, history of prior cancers ($P = 0.13$). A summary of patients clinicopathologic characteristics by ER status is presented in table 1. Distant metastatic disease to the lung only occurred in one patient (7%) with ER-positive tumors compared to ER-negative tumors in which 17 (15%) patients had distant metastatic disease to the lung, brain, liver, adrenal gland, bone, and pancreas (Table 2) ($P = 0.69$).

All patients were treated with either partial or complete mastectomies. However, 101 (81%) patients received additional treatment in the form of chemotherapy, radiotherapy, hormonal therapy and, neoadjuvant therapy in varying combinations. There was no record of additional treatment in 24 (19%) patients. Ten (67%) patients with ER-positive tumors and 81 (74%) patients with ER-negative tumors received chemotherapy respectively ($P = 0.55$). Nine (60%) patients with ER-positive tumors and 61 (55%) patients with ER-negative tumors received additional radiotherapy respectively ($P = 0.79$). Nine (60%) patients with ER-positive tumors received hormonal therapy and 17 (15%) patients with ER-negative tumors received hormonal therapy and this difference in hormonal treatment was statistically significant ($P<0.001$). Six (40%) patients with ER-positive tumors and 25 (23%) patients with ER-negative tumors received neoadjuvant therapy ($P = 0.20$). Following neoadjuvant therapy, only one (17%) patient with ER-positive tumors had a complete pathologic response, compared with 5 (20%) patients with ER-negative tumors who had a complete pathologic response ($P>0.99$). The 10-year OS for ER-positive tumors was 100% (95% CI, 100–100) and that for ER-negative tumors was 82.09% (95% CI, 71.94–93.67). However, this difference in survival curves between ER-positive and ER-negative tumors was not

statistically significant (HR = 0.35; 95% CI, 0.003–2.67; $P = 0.39$) (Fig. 9). When adjusted by tumor size, histology (heterologous histology vs. others), stage (I-II vs. III-IV), metastatic disease, lymphovascular invasion, neoadjuvant therapy, hormonal treatment, progesterone receptor, chemotherapy and smoking, multivariable firth Cox proportional hazard regression analysis by ER status, showed no significant difference in OS between ER-positive and ER-negative tumors (HR = 1.84; 95% CI, 0.01–19.65; $P = 0.75$) (Table 3).

Discussion

Our study is unique because it is one of few studies to describe the prognostic relevance of ER status in MBC and provides additional clinicopathologic information that may guide future research and management of patients with this rare disease. We have previously described our experience with MBC as a rare subtype of breast cancer. [10] However, in the current study, we have provided additional clinical information on the relevance of ER status in MBC, given that most cases are triple-negative. Following our review, the median age at diagnosis for all MBC patients was 57 years and this finding is similar to what has been previously reported in other studies. [16, 17]. When stratified by ER status, we found no significant difference in age of occurrence between ER-positive and ER-negative tumors. We found MBC to be more common in Black/AA women (57%), compared with White/Caucasian women (34%) and women from other ethnicities (9%). Even though this difference by race/ethnicity was not statistically significant, our findings of MBC being more prevalent in Black/AA women is consistent with the experiences from similar studies. [8, 18] Additionally, our experience may be explained by the strategic location of our institution with a predominantly Black population in the Metropolitan city of Detroit, in Michigan United States. When stratified by ER status however, we found no significant difference in MBC occurrence by race/ethnicity.

We also found no statistical differences in size between ER-positive and ER-negative tumors, underscoring the fact that the biological characteristics that drives this class of tumors may be independent of their hormone receptor statuses. This however leaves room for further research. In terms of histologic grade (most tumors were high grade regardless of hormone status), histologic subtype (heterologous histology was more common in both groups), and clinical stage (stage II disease was more common in both groups), there was no difference between ER-positive and ER-negative tumors. Additionally, there was no difference between ER-positive and ER-negative tumors in terms of nodal disease or lymphovascular invasion. Some previous studies which evaluated hormone receptor (ER+/PR+, ER+/PR−, ER−/PR+ and ER−/ PR−) status in MBC found no significant differences between hormone positive MBC and hormone negative MBC. [19, 20] The findings from previous studies are consistent with our experience in patients with MBC, in which ER-positivity appears to have no prognostic relevance in patients with this rare disease.

Regardless of hormonal status, all patients with MBC from our cohort were treated with either partial or complete mastectomy. Of note is that patients with ER-positive tumors were more likely to be PR-positive and more likely to be treated with hormonal therapy, compared with patients with ER-negative tumors and this finding was statistically significant. The clinical impact of this observation is not exactly clear to us, as addition

of hormonal therapy to ER-positive tumors did not provide a survival advantage in this group. However, additional studies (particularly prospective studies) are needed to validate our observations. No statistically significant differences were observed between ER-positive and ER-negative tumors following chemotherapy and radiotherapy treatments; thus, these treatment modalities may be individually selected based on the patients' clinicopathologic characteristics. Based on our findings, the clinical utility of neoadjuvant therapy in MBC patients may be up for debate, as the pathologic complete response in both ER-positive (17%) and ER-negative (20%) tumors produced statistically insignificant results. We, therefore, hypothesize that due to the biologically aggressive nature of these tumors, patients may be better managed initially with surgery, followed by adjuvant therapy. However, additional studies are needed to characterize our observations. After adjusting for several clinicopathologic variables, multivariable firth Cox proportional hazard regression analysis by ER status showed no difference in OS between ER-positive and ER-negative tumors. This suggests that MBCs are generally aggressive tumors with unfavorable outcomes, regardless of their hormonal profiles, in this case, their ER positivity status.

We acknowledge that the retrospective nature of our study limits the interpretation of our findings and their application in prospective patients with MBC. However, this is not unexpected as the ability to conduct prospective clinical trials with MBC patients remains challenging due to its rare and aggressive nature. However, despite this obvious limitation, our study remains one amongst few other studies to characterize the prognostic relevance of hormone expression in MBC, in this case the ER status. Findings from this study may serve as a foundation upon which future research may be conducted with potential management benefits for patients with MBC.

Data access statement

Research data supporting this publication are submitted as a part of this work.

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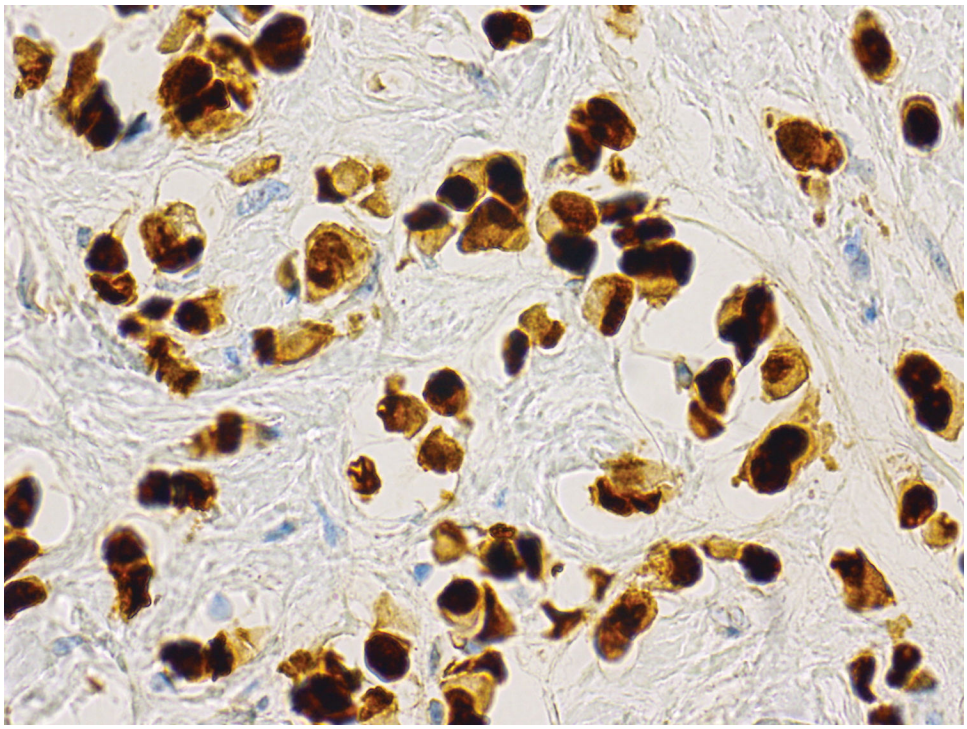

Fig. 1.
Metaplastic Breast Carcinoma showing ER positivity > 10% (40X magnification).

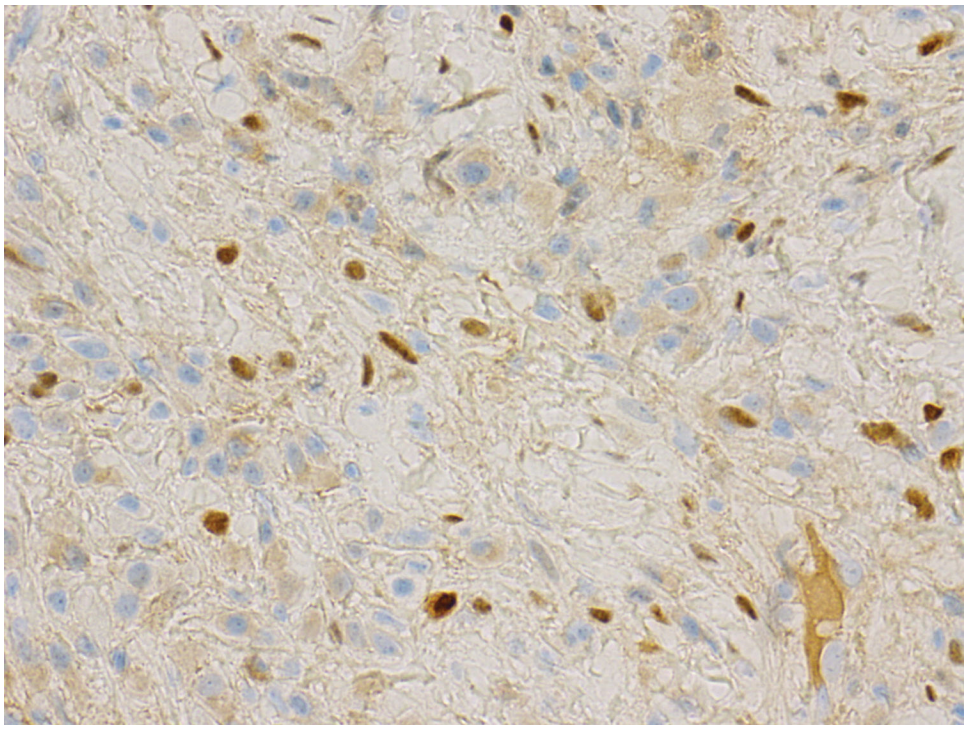

Fig. 2.
Metaplastic Breast Carcinoma showing ER positivity ≤ 10% (40X magnification).

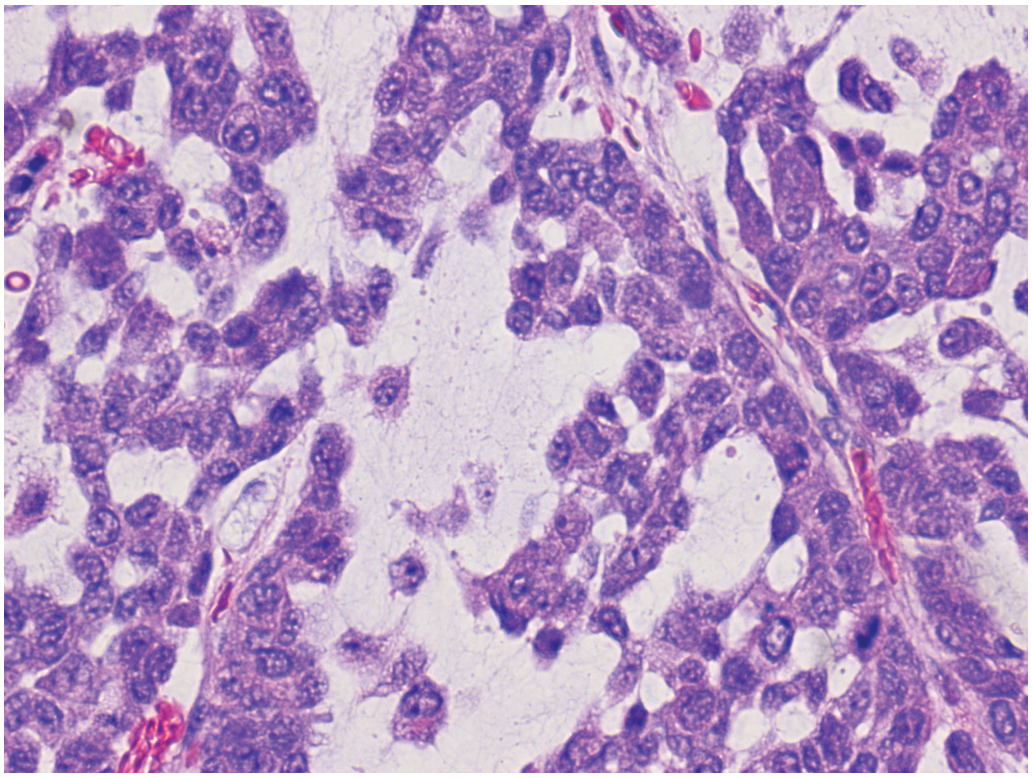

Fig. 3.
Metaplastic Breast Carcinoma with chondroid differentiation (40X magnification).

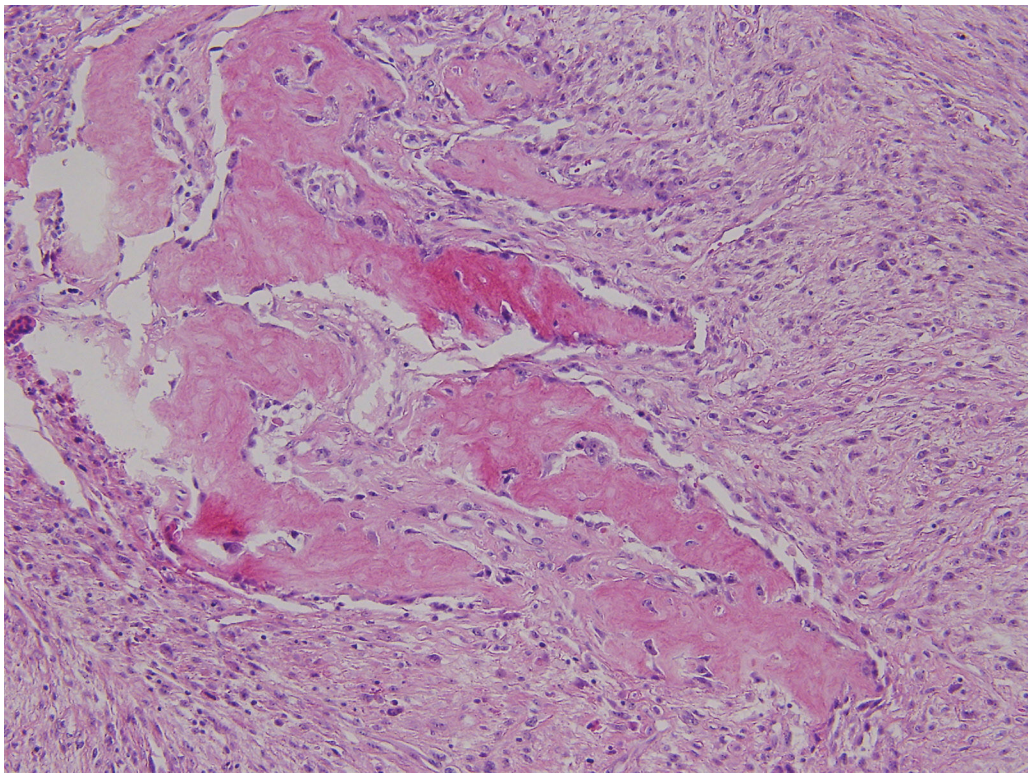

Fig. 4.
Metaplastic Breast Carcinoma with rhabdoid differentiation (40X magnification).

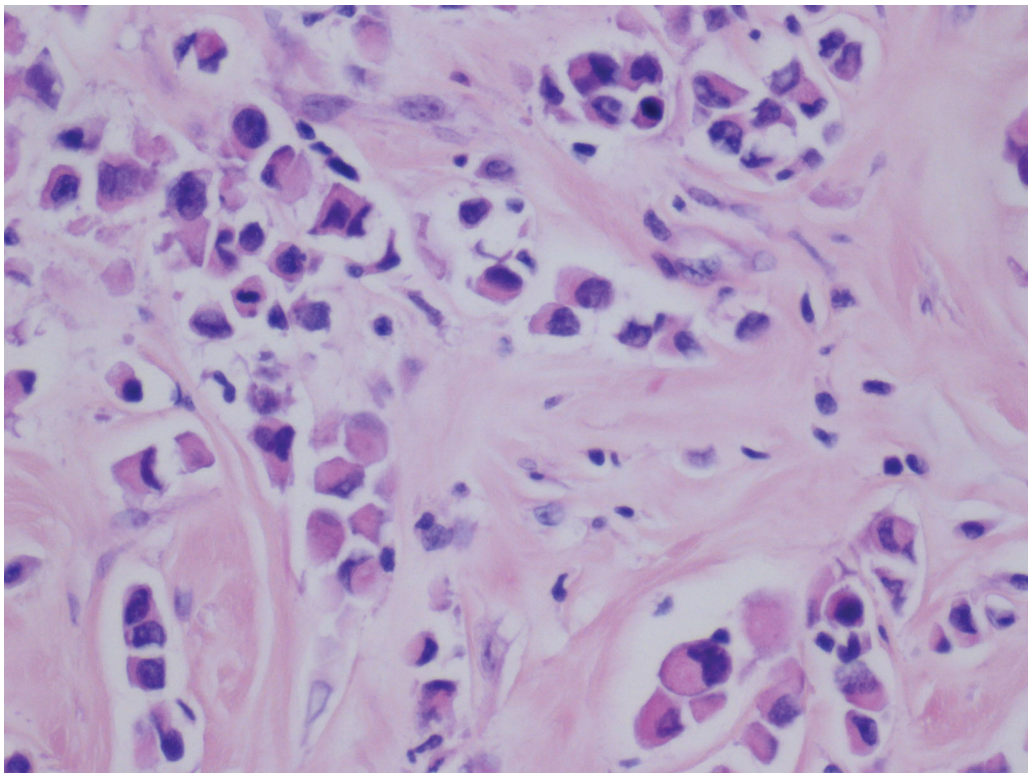

Fig. 5.
Metaplastic Breast Carcinoma with osteoid differentiation (40X magnification).

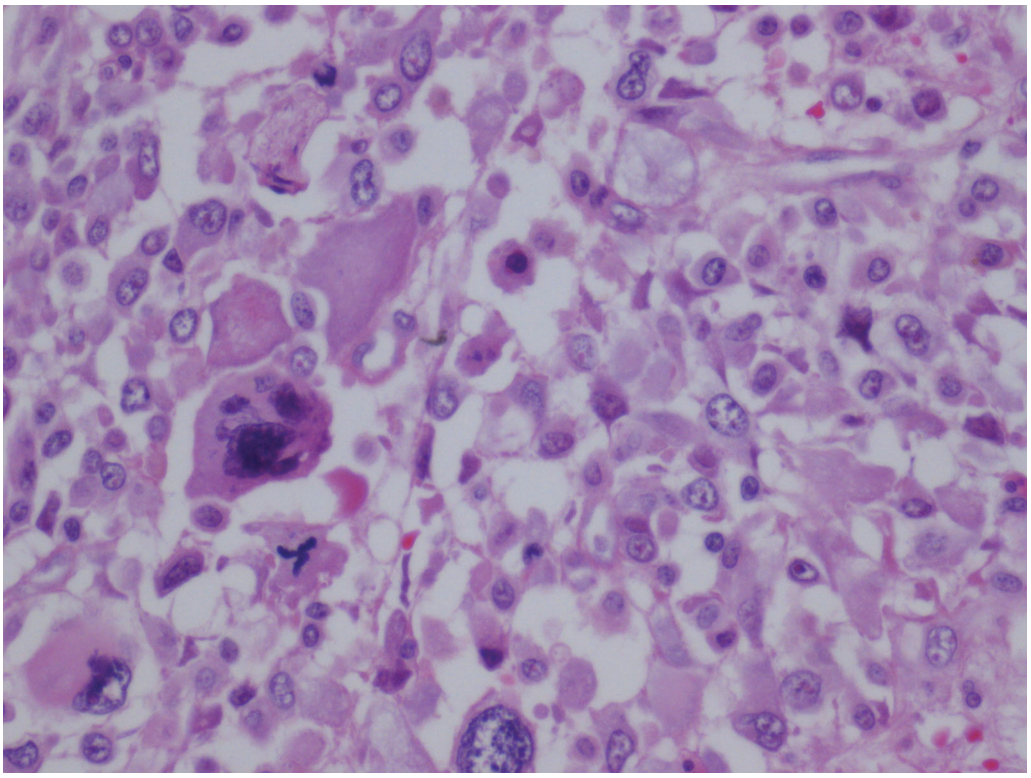

Fig. 6.
Metaplastic Breast Carcinoma with osteoclastic-type giant cells (40X magnification).

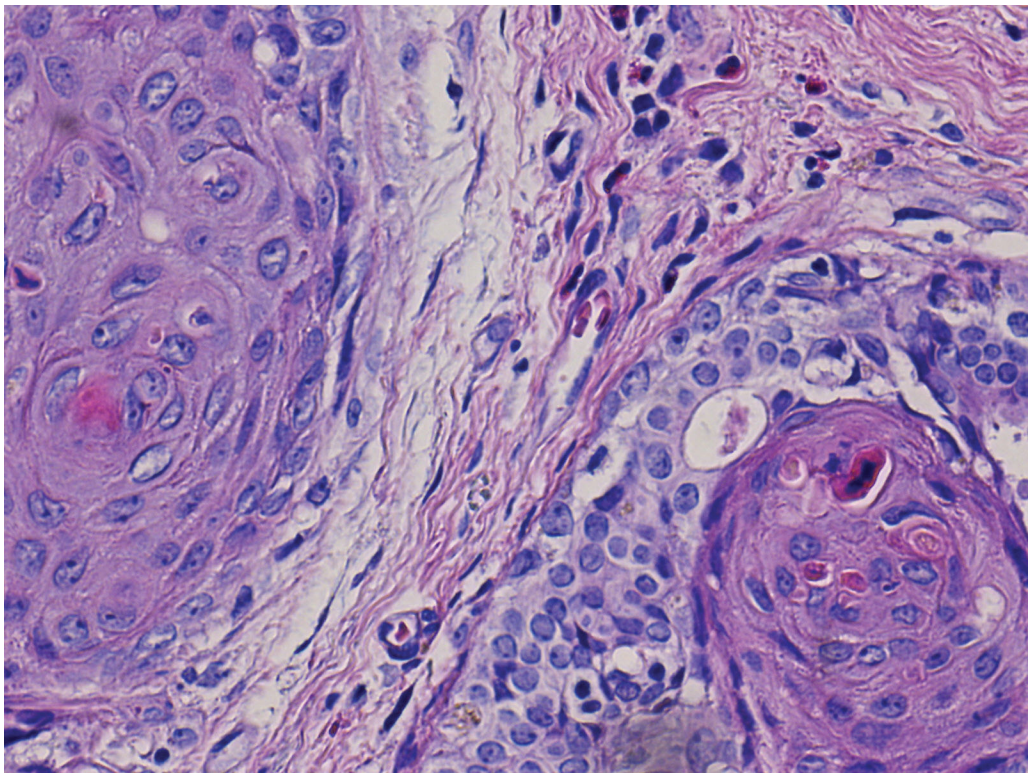

Fig. 7.
Metaplastic Breast Carcinoma with squamous cell carcinoma (40X magnification).

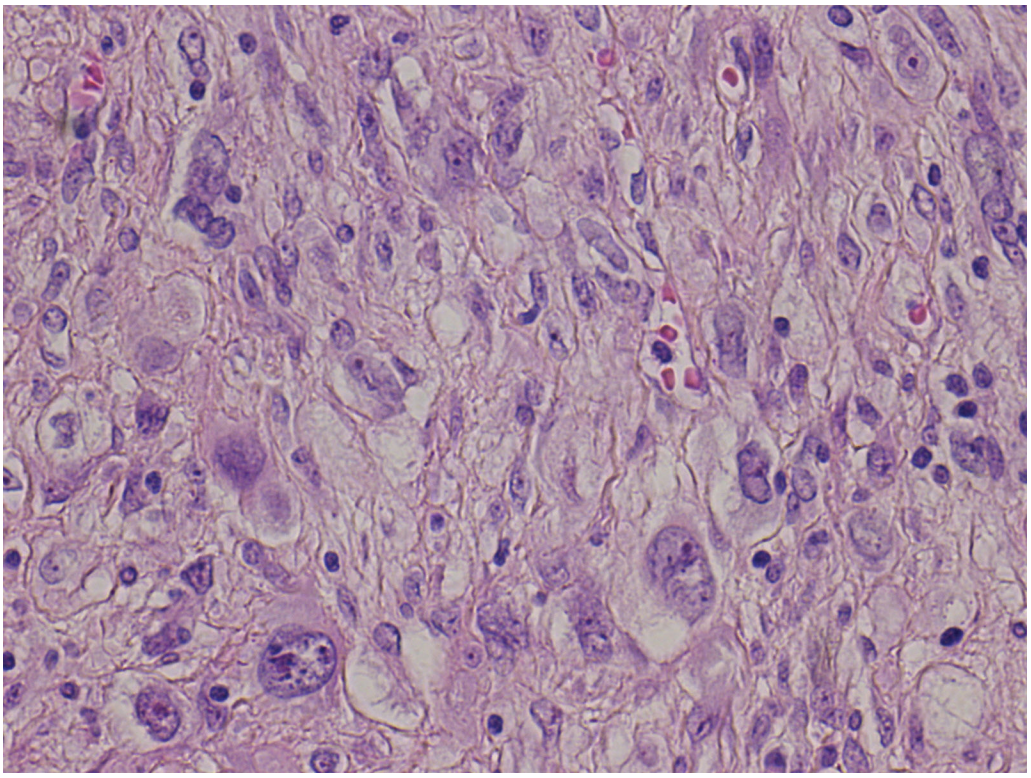

Fig. 8.
Metaplastic Breast Carcinoma with poorly differentiated spindle cells (40X magnification).

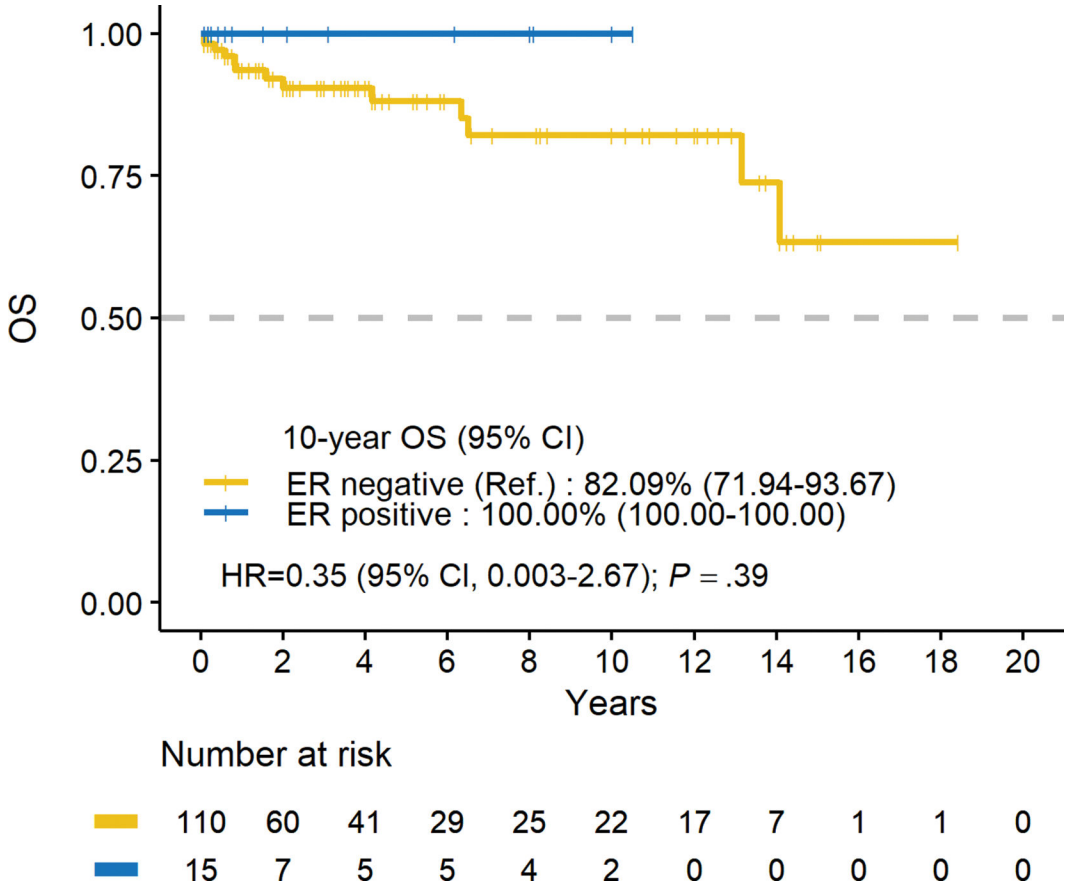

Fig. 9.
Kaplan-Meier curve of overall survival (OS) by estrogen receptor (ER) status.

Table 1

Patient characteristics by estrogen receptor (ER).

Variable	All (n = 125)	ER Negative (n = 110)	ER Positive (n = 15)	P value *
Age at diagnosis, year - median (range)	57 (27,92)	57 (27,92)	53 (33,88)	.27
Race - no. (%)				>0.99
White	43 (34)	38 (35)	5 (33)	
African American	71 (57)	62 (56)	9 (60)	
Other	11 (9)	10 (9)	1 (7)	
Tumor size (cm) - median (range)	3 (0.5,21.5)	3.05 (0.5,21.5)	2.5 (0.6,11.5)	.82
Histologic grade - no. (%)				.34
Low	3 (2)	2 (2)	1 (7)	
Intermediate	7 (6)	6 (5)	1 (7)	
High	115 (92)	102 (93)	13 (87)	
Histologic subtype - no. (%)				.65
Squamous component only	36 (29)	31 (28)	5 (33)	
Spindle/Sarcomatoid component only	32 (26)	30 (27)	2 (13)	
Heterologous	38 (30)	32 (29)	6 (40)	
Mixed squamous	19 (15)	17 (15)	2 (13)	
AJCC stage - no. (%)				>0.99
Stage I	27 (22)	24 (22)	3 (20)	
Stage II	59 (47)	51 (46)	8 (53)	
Stage III	21 (17)	19 (17)	2 (13)	
Stage IV	18 (14)	16 (15)	2 (13)	
HER2 - no. (%)				.29
Positive	9 (7)	7 (6)	2 (13)	
Negative	116 (93)	103 (94)	13 (87)	
Progesterone receptor - no. (%)				***<0.001***
Positive	17 (14)	8 (7)	9 (60)	
Negative	108 (86)	102 (93)	6 (40)	
Metastatic disease - no. (%)				.69
Yes	18 (14)	17 (15)	1 (7)	
No	107 (86)	93 (85)	14 (93)	.36
Positive lymph nodes - no. (%)				
Yes	35 (28)	29 (26)	6 (40)	
No	90 (72)	81 (74)	9 (60)	
Lymphovascular invasion - no. (%)				>0.99
Yes	33 (26)	29 (26)	4 (27)	
No	92 (74)	81 (74)	11 (73)	
Disease focality - no. (%)				.72
Unifocal	104 (83)	92 (84)	12 (80)	
Multifocal	21 (17)	18 (16)	3 (20)	
Ductal carcinoma in situ (DCIS) - no. (%)				.57

Yes	47 (38)	40 (36)	7 (47)	
No	78 (62)	70 (64)	8 (53)	
Fibrocystic breast disease - no. (%)				.14
Yes	22 (18)	17 (15)	5 (33)	
No	103 (82)	93 (85)	10 (67)	
Variable	**All (*n* = 125)**	**ER Negative (*n* = 110)**	**ER Positive (*n* = 15)**	**P value** *
Obesity/Overweight - no. (%)				>0.99
Yes	75 (60)	66 (60)	9 (60)	
No	50 (40)	44 (40)	6 (40)	
Smoking - no. (%)				.09
Yes	53 (42)	50 (45)	3 (20)	
No	72 (58)	60 (55)	12 (80)	
History of prior cancer - no. (%)				.13
Yes	20 (16)	20 (18)	0 (0)	
No	105 (84)	90 (82)	15 (100)	
Treatment - no. (%)				.18
Not recorded	24 (19)	22 (20)	2 (13)	
Treated with chemotherapy	91 (73)	81 (74)	10 (67)	
Treated without chemotherapy	10 (8)	7 (6)	3 (20)	
Chemotherapy - no. (%)				.55
Yes	91 (73)	81 (74)	10 (67)	
No	34 (27)	29 (26)	5 (33)	
Radiation therapy - no. (%)				.79
Yes	70 (56)	61 (55)	9 (60)	
No	55 (44)	49 (45)	6 (40)	
Hormonal therapy - no. (%)				***<0.001***
Yes	26 (21)	17 (15)	9 (60)	
No	99 (79)	93 (85)	6 (40)	
Neoadjuvant therapy - no. (%)				.20
Yes	31 (25)	25 (23)	6 (40)	
Pathologic complete response				>0.99
Yes	6 (19)	5 (20)	1 (17)	
No	25 (81)	20 (80)	5 (83)	
No	94 (75)	85 (77)	9 (60)	

* P value is calculated by Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

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Table 2

Metastatic disease.

Metastatic site	All (*n*= 18)	ER negative (*n* = 17)	ER positive (*n* = 1)
Lung	15 (83%)	14 (82%)	1 (100%)
Brain	5 (28%)	5 (29%)	0 (0%)
Liver	3 (17%)	3 (18%)	0 (0%)
Adrenal	1 (6%)	1 (6%)	0 (0%)
Bone	1 (6%)	1 (6%)	0 (0%)
Pancreas	1 (6%)	1 (6%)	0 (0%)

Table 3

Univariable and multivariable firth Cox proportional hazard regression analysis of overall survival (OS) by estrogen receptor (ER).

	Univariable *		Multivariable#	
	HR (95% CI)	P value	HR (95% CI)	P value
Estrogen receptor				
Negative	Ref.		Ref.	
Positive	0.35 (0.003–2.67)	.39	1.84 (0.01–19.65)	.75

OS, overall survival; HR, Hazard ratio; CI, Confidence interval.

*Univariable firth Cox regression analysis.

#Multivariable firth Cox regression analysis by propensity score-based covariate adjustment with tumor size, histology (heterologous histology vs. others), stage (I-II vs. II-IV), metastatic disease, lymphovascular invasion, neoadjuvant therapy, hormonal treatment, progesterone receptor, chemotherapy and smoking.