Metaplastic Breast Cancer: Mesenchymal Subtype Has Worse Survival Outcomes

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Abstract

Purpose

Metaplastic breast carcinoma (MBC) is a rare type of breast cancer that accounts for 0.2-1% of all breast cancers. To date, there are only few institutional studies comparing survival rates between different subtypes. In this retrospective cohort study, we aim to evaluate factors effecting survival rates of different subtypes of MBC.

Methods

This retrospective cohort study observed 118 non-metastatic MBC patients record extracted from 15,244 breast cancer cases between December 2000 and December 2020. In order to analyse factors effecting survival rates of mesenchymal subtype of MBC, all cases are classified as mesenchymal (n=45) and other (n=48). Twenty-five cases that could not be sub-classified due to the missing data. Univariate and multivariate logistic regression analysis were performed to define factors associated with survival rates.

Results

Of the 15,244 cases, 118 (0.8%) were non-metastatic MBC. 105 were triple negative and 12 were non-luminal HER2. There was no significant difference between mesenchymal and other subgroups for age, median tumour size, AJCC staging, and type of surgery. Of the five local recurrences with known subgroup, four of them had mesenchymal subtype. It is demonstrated that mesenchymal subtype was significantly associated with worse 5-year disease-free survival and disease specific survival (HR: 2.35 [1.01-5.48], p=0.049 and HR: 3.16 [1.06-9.47], p=0.040 with 95% CI respectively).

Conclusion

This study is one of the few studies presenting the survival outcomes of subtypes of MBCs. Nonetheless, it is the only study demonstrating that mesenchymal subtype had worse survival outcomes. Further studies are needed to determine the outcome of different subtypes of MBCs.

1. Introduction

Metaplastic breast carcinoma (MBC) is a rare type of breast cancer that accounts for 0.2-1% of all breast cancers [1]. It was first described in 1973 but recognized as a new breast cancer subtype by World Health Organization in 2000 [2]. It is basically described as squamous or mesenchymal differentiation of neoplastic epithelium to a non-glandular component and histologically classified as low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with heterologous mesenchymal differentiation and mixed metaplastic carcinoma [3]. Those subtypes including squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation are considered as the aggressive subtypes. They are more aggressive and more prone to make metastasis than invasive ductal type breast cancers including triple negative breast cancers (TNBC) [4, 5]. It usually spreads hematogenously rather than lymphatically [6–8]. MBCs are generally triple negative and they are associated with higher tumour (T) stage and less nodal involvement at presentation [9].

In the recent literature, there is a lack of information about survival rates of different subtypes of MBC. To date, there are only few institutional studies comparing survival rates between different subtypes [10–12]. In this retrospective cohort study, we aim to evaluate factors effecting survival rates of different subtypes of MBC.

2. Material And Methods

2.1 Patient Cohort and Data Collection

This retrospective cohort study is planned to evaluate patients with a pathologic diagnosis of MBC. A total of 15,244 breast cancer patient records between December 2000 and December 2020 were evaluated. Patients with American Joint Committee on Cancer (AJCC) stage IV diseases and missing data were excluded. Finally, 118 MBC patients were extracted from institutional database.

Surgical procedure was planned as mastectomy or breast conserving surgery depending on clinical presentation of the patient. Adjuvant or neoadjuvant therapies were individually decided in a multidisciplinary breast surgical oncology meeting. Chemotherapy regimens and radiotherapy procedure was decided concordant with up-to-date guidelines. Main chemotherapy regimen was anthracycline and alkylating agents like cyclophosphamide followed by taxanes. If the patient is HER2 positive a monoclonal antibody like trastuzumab was administered.

2.2 Definitions and Statistical Analysis

Overall survival (OS) is defined as the length of time from the date of diagnosis to death from any cause or to date of last follow-up. Disease-free survival (DFS) is defined as the time from diagnosis until recurrence of tumour or death from any cause. Disease specific survival (DSS) is defined as the length of time from the date of diagnosis to death from disease or to date of last follow-up. Locoregional recurrence-free survival (LRFS) is defined as the length of time from the date of diagnosis to the development of new tumour in ipsilateral breast, chest or regional lymph nodes.

In order to analyse factors effecting survival rates of mesenchymal subtype of MBC, all cases are classified as mesenchymal (n=45) and other (n=48). In the other group there are squamous cell MBC (n=43), spindle cell MBC (n=3), and mixed type MBC (n=2). Of those, 25 cases that could not be sub-classified due to the missing data are not included in the analysis regarding subgroups.

To assess differences in categorical and continuous variables, Chi-squared tests (Pearson Chi-Square, Continuity Correction, Fisher's Exact Test) and Mann-Whitney U test were used. Survival rates were analysed using Kaplan-Meier method and log rank test was issued in order to analyse the effect of patient demographics and pathologic features on survival rates. Univariate and multivariate logistic regression analysis were performed to define factors associated with survival rates. All p-values were two-sided and a p-value of <0.05 with a 95% confidence interval (CI) was considered as significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) Windows software version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

Of the 15,244 breast cancer patients recorded between December 2000 and December 2020, 118 (0.8%) were non-metastatic metaplastic breast cancer. Two patients with AJCC stage IV disease were excluded. Median age was 48 (27-84). Almost two-thirds of the patients were T2 without axillary involvement. Of those, 72 patients (61%)

underwent breast conserving surgery (BCS), whereas mastectomy was performed in the remaining cases (39%). All patients received systemic therapy and 16 of them received neoadjuvant chemotherapy. Of the 117 cases with known receptor status, 105 were triple negative and 12 were non-luminal HER2. There were no cases with hormone receptor positivity (Table 1). As described before, metaplastic carcinomas were stratified as mesenchymal for 45 (48.4%) and other for 48 (51.6%). In the subgroup analysis, there was no statistical significant difference between mesenchymal and other subgroups for age, median tumour size, AJCC staging, and type of surgery (Table 2).

Table 1
Demographic and pathologic features of cases (n=118).

Factors	Category	n	%
Median Age		48 (27-84)	
	≤40	31	26.3
	>40	87	73.7
	<50	62	52.5
	≥50	56	47.5
Median Tumor Diameter (mm)		30 (8-140)	
pT Stage	I	25	21.2
	II	73	61.9
	III	17	14.4
	IV	3	2.5
pN Stage	0	75	63.6
	I	29	24.6
	II	8	6.8
	III	6	5.1
pStage	I-IIA	71	60.2
	IIB-IIIC	47	39.8
Operation Type	BCS	72	61.0
	Mastectomy	46	39.0
Axillary Surgery	SLNB	72	61.0
	SLNB + ALND	26	22.0
	ALND	20	16.9
NCT	Yes	16	13.6
	No	102	86.4
Systemic Treatment	CT (+) / RT (-)	11	9.3
	CT (+) / RT (+)	107	90.7
Grade	II	3	2.5
	III	115	97.5

BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2, TN: Triple negative.

Factors	Category	n	%
LVI	+	78	66.1
	-	40	33.9
HER2 (n=117)	-	105	89.7
	+	12	10.3
Molecular Subtype (n=117)	TN	105	89.7
	Non-Luminal HER2 (+)	12	10.3
Median Ki67 score (%) (n=96)		70 (range, 20-90)	
Metaplastic Subtype (n=93)	Mesenchymal	45	48.4
	Other	48	51.6
BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2, TN: Triple negative.			

Table 2
Demographic and pathologic features of cases depending on metaplastic breast cancer subtypes (n=93)

		All	Mesenchymal	Other	
			(n=45)	(n=48)	
Factors	Category	n	n (%)	n (%)	p
Median Age (range)	All	93	46 (27-77)	49 (30-84)	0.224 ^a
	<50	41	17 (37.8)	24 (50.0)	0.328 ^a
	≥50	52	28 (62.2)	24 (50.0)	
Median Tumor size (mm)		30	31 (10-140)	30 (10-130)	0.969 ^a
pT	I-II	79	40 (88.9)	39 (81.3)	0.389 ^b
	III-IV	14	5 (11.1)	9 (18.8)	
pN	0	61	31 (68.9)	30 (62.5)	0.667 ^b
	I-III	32	14 (31.1)	18 (37.5)	
pStage	I-IIA	57	30 (66.7)	27 (56.3)	0.414 ^b
	IIB-IIIC	36	15 (33.3)	21 (43.8)	
Surgery Type	BCS	57	28 (62.2)	29 (60.4)	0.999 ^b
	Mastectomy	36	17 (37.8)	19 (39.6)	
Axillary Surgery	SLNB	55	28 (62.2)	27 (56.3)	0.708 ^b
	SLNB+ALND / ALND	38	17 (37.8)	21 (43.8)	
NCT	Yes	9	4 (8.9)	5 (10.4)	0.999 ^b
	No	84	41 (91.1)	43 (89.6)	
Systemic Treatment	CT (+) / RT (-)	9	6 (13.3)	3 (6.3)	0.307 ^b
	CT (+) / RT (+)	84	39 (86.7)	45 (93.8)	
Grade	II	3	1 (2.2)	2 (4.2)	0.999 ^b
	III	90	44 (97.8)	46 (95.8)	
LVI	Yes	33	13 (28.9)	20 (41.7)	0.285 ^b
	No	60	32 (71.1)	28 (58.3)	

p>0.05; **a**: Mann-Whitney U Test; **b**: Chi-Square Test

BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, NCT: Neoadjuvant chemotherapy, CT: Chemotherapy, RT: Radiotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2.

		All	Mesenchymal (n=45)	Other (n=48)	
Molecular Subtype (n=92)	Triple negative	87	44 (100.0)	43 (89.6)	0.057 ^b
	Non-Luminal HER2 (+)	5	0 (0.0)	5 (10.4)	
Mean Ki67 score (n=96)		74	70.61±15.95	63.05±18.26	0.052 ^a
p>0.05; a : Mann-Whitney U Test; b : Chi-Square Test					
BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, NCT: Neoadjuvant chemotherapy, CT: Chemotherapy, RT: Radiotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2.					

Median follow-up time was 57 months. 5-year OS is 80%. The DFS, DSS, and LRFS rates were 76.2%, 82.4%, and 93.5% respectively. There were only seven local-regional recurrences, which two of them were chest wall and five of them were in breast. No axillary recurrence was observed in our series. Of the five local recurrences with known subgroup, four of them had mesenchymal subtype. Significant factors effecting DFS, and DSS in univariate Cox regression analysis (Table 3) were further analysed in multivariate Cox proportional hazard regression model (Table 4). The 5-year DFS was 69.3% vs 86.2%, DSS was 77.8% vs 88.2%, and LRFS was 91.6% vs 97.8% for mesenchymal vs other subtypes of MBC respectively. Our results have demonstrated that mesenchymal subtype was significantly associated with worse 5-year DFS and DSS (HR: 2.35 [1.01-5.48], p=0.049 and HR: 3.16 [1.06-9.47], p=0.040 with 95% CI respectively).

Table 3
Factors affecting 5-year Loco-regional recurrence free survival, disease free survival and disease specific survival (Univariate Cox Regression analysis).

(Univariate Cox Regression analysis).									
	5-year DFS			5-year DSS			5-year LRFS		
Factors	HR (95%CI)	p	%	HR (95%CI)	p	%	HR (95%CI)	p	%
Age		0.475			0.221			0.882	
<50	1.34 (0.60- 2.98)		73.8	1.85 (0.69- 4.92)		78.5	1.13 (0.23- 5.60)		93.9
≥50	Reference (1)		79.0	Reference (1)		86.5	Reference (1)		95.8
pT stage		0.008*			0.001*			0.819	
I-II	Reference (1)		90.5	Reference (1)		93.3	Reference (1)		95.0
III-IV	3.19 (1.36- 7.45)		55.0	4.99 (1.95- 12.75)		57.0	1.29 (0.15- 11.02)		94.1
pN stage		<0.001*			<0.001*			0.300	
0	Reference (1)		90.6	Reference (1)		96.2	Reference (1)		95.1
I-III	5.69 (2.36- 13.69)		52.3	16.34 (3.75- 71.16)		59.1	2.35 (0.47- 11.81)		91.8
pStage		<0.001*			<0.001*			0.397	
I-IIA	Reference (1)		90.1	Reference (1)		96.0	Reference (1)		94.9
IIB-IIIC	4.89 (2.04- 11.76)		55.8	14.06 (3.23- 61.23)		62.4	2.01 (0.40- 10.04)		92.5
Surgery Type		0.063			0.016*			0.991	
BCS	Reference (1)		82.3	Reference (1)		89.3	1.01 (0.18- 5.54)		93.2
Mastectomy	2.11 (0.96- 4.64)		66.6	3.24 (1.25- 8.42)		71.1	Reference (1)		95.2

*:p<0.05; Cox Regression Analysis

DFS: Disease-free survival, DSS: Disease-specific survival, LRFS: Locoregional recurrence-free survival, HR: Hazards ratio, CI: Confidence interval, BCS: Breast conserving surgery, NCT: Neoadjuvant chemotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2.

	5-year DFS		5-year DSS		5-year LRFS	
NCT	<0.001*		<0.001*		0.014*	
+	7.43 (2.97- 18.58)	50.5	6.56 (2.39- 17.98)	54.2	9.52 (1.59- 57.06)	83.3
-	Reference (1)	80.9	Reference (1)	86.5	Reference (1)	95.1
LVI	<0.001*		0.001*		0.343	
+	3.63 (1.59- 8.23)	58.8	6.78 (2.23- 20.60)	65.2	2.18 (0.44- 10.82)	91.7
-	Reference (1)	87.0	Reference (1)	92.4	Reference (1)	94.9
Molecular Subtype	0.816		0.399		0.079	
Triple negative	1.19 (0.28- 5.05)	76.0	2.37 (0.32- 17.69)	81.2	Reference (1)	95.3
Non-Luminal HER2 (+)	Reference (1)	78.8	Reference (1)	90.9	4.58 (0.84- 24.99)	90.0
Ki67	0.766		0.679		0.672	
≤70%	Reference (1)	82.9	Reference (1)	88.1	Reference (1)	95.6
>70%	1.16 (0.43- 3.12)	79.8	1.29 (0.39- 4.21)	86.0	1.53 (0.22- 10.84)	93.9
Metaplastic Subtype	0.092		0.240		0.214	
Mesenchymal	2.24 (0.85- 5.91)	69.3	1.91 (0.64- 5.69)	77.8	4.02 (0.45- 36.16)	91.6
Other	Reference (1)	86.2	Reference (1)	88.2	Reference (1)	97.8
*:p<0.05; Cox Regression Analysis						
DFS: Disease-free survival, DSS: Disease-specific survival, LRFS: Locoregional recurrence-free survival, HR: Hazards ratio, CI: Confidence interval, BCS: Breast conserving surgery, NCT: Neoadjuvant chemotherapy, LVI: Lymphovascular invasion, HER2: Human epidermal growth receptor-2.						

Table 4
Cox proportional hazards regression model assessing factors associated with disease free and disease specific survival.

Factors	Disease Free Survival (DFS)	p	Disease Specific Survival (DSS)	p
	HR (95%CI)		HR (95%CI)	
Age		0.343		0.091
<50	1.49 (0.65-3.41)		2.44 (0.87-6.88)	
≥50	Reference (1)		Reference (1)	
pT stage		0.024		0.002
I-II	Reference (1)		Reference (1)	
III-IV	3.0 (1.16-7.79)		5.92 (1.89-18.57)	
pN stage		0.002		0.001
N0	Reference (1)		Reference (1)	
N1-3	5.01 (1.76-14.21)		15.30 (3.03-77.36)	
LVI		0.670		0.719
-	Reference (1)		Reference (1)	
+	1.24 (0.46-3.39)		1.26 (0.36-4.43)	
Metaplastic Subtype		0.049		0.040
Mesenchymal	2.35 (1.01-5.48)		3.16 (1.06-9.47)	
Other	Reference (1)		Reference (1)	
Hazard ratio (HR) are presented with their 95% confidence interval (CI) and the p-value				
Cox Regression analysis, (<i>Method = Enter</i>)				
DFS: Disease-free survival, DSS: Disease-specific survival, LVI: Lymphovascular invasion.				

4. Discussion

In the up-to-date literature, there is a lack of information about clinicopathologic features and survivals of different subtypes of MBC. Few studies only emphasizes this topic [10–16]. Almost all of the studies gives information solely about MBC or compares differences between MBC and TNBC [17–19]. In these studies [9, 20, 21], researchers determined that MBC is generally larger in tumour size and presents lower nodal involvement. Conversely, it is diagnosed at more advanced stages, has worse survival rates, more resistant to adjuvant therapies when compared to other subtypes of breast cancer. Additionally, MBCs are generally triple negative subtype. In this study, we do not compare MBC and TNBC. Alternatively, we aim to focus on factors effecting survival rates of different subtypes of MBCs and specifically comparing mesenchymal subtype and others.

There are prominent features that effects survival rates in different types of breast cancer. In a recent National Cancer Data Base (NCDB) analysis of 2,084 MBCs, higher T stage, nodal involvement, and lymphovascular invasion is correlated with worse outcomes [9]. Moreover, MBC had worse unadjusted overall survival when compared with TNBC and other types of breast cancer regardless of clinical stage. Same in our study, higher T stage, nodal involvement and lymphovascular invasion is significantly correlated with worse 5-year DFS and DSS (Table 3). A Surveillance, Epidemiology, and End Results (SEER) analysis by Schroeder et al [22] demonstrated that HER2 positive MBCs are associated with better survival compared to triple negative MBCs in a multivariate Cox regression model. We did not identify any survival difference between triple negative and HER2 positive MBC subtypes.

As WHO recognise it as a new subtype in 2000 [1], there has always been a debate on subtypes of MBCs. It is a rare type of breast cancer so that there are few cases and few studies on this topic. Lee et al presented that squamous and spindle cell differentiation were associated with poorer survivals than other types of MBCs [23]. Cimino-Mathews and colleagues also demonstrated that there was no OS and LRFS difference between mixed subtypes and non-mixed subtypes of MBCs but distant metastasis-free survival was significantly worse for mixed subtypes [24]. A multi institutional study found that matrix-producing carcinomas presented better survival than spindle, squamous, and mixed histologic subtypes in a series of 283 patients [4]. The most recent and detailed analysis about survival of different subtypes of MBCs were presented by Tadros et al. [10]. They analysed 132 MBC patients which 45 were heterologous mesenchymal (34.1%), 26 were squamous (19.7%), 26 were spindle (19.7%), and 30 were mixed (22.7%) subtype. They found that squamous subtype had the worse OS (50%; 95% CI, 26–73%) and DSS (56%; 95% CI, 32–79%). Heterologous mesenchymal subtype had the best OS (76%; 95% CI, 68–84%) and DSS (79%; 95% CI, 71–87%). In our series of 118 MBCs, we identified 93 cases with known subtype. They were stratified as 45 (48.4%) mesenchymal and 48 (51.6%) as other (squamous [n=43], spindle [n=3], and mixt [n=2]). In Cox proportional hazard regression model, we found that mesenchymal subtype had the worse DFS (HR: 2.35; %95 CI, 1.01-5.48, p=0.049) and DSS (HR: 3.16; %95 CI, 1.06-9.47, p=0.040) than other subtypes. These results are different from published series by Tadros and colleagues [10]. Although we grouped squamous together with spindle and mixt subtype, most of the cases were squamous. Besides, the significant worse DFS and DSS of mesenchymal subtype did not change even after comparing solely mesenchymal and squamous subtypes. Another aspect of the discussion is the debate on how to classify subtypes of MBCs. It is first described in 2000 and there has been major changes on its sub-classification [1]. This means the classification of tumour subtypes in MBC may differ from institution to institution. As it is classified as heterologous mesenchymal in previous study [10], we classified it as purely mesenchymal.

There are some limitations of the present study. First, this is a retrospective analysis and it has small number of cases. However, it is still one of the largest series about subtypes of MBCs in the literature. Another limitation is the classification of MBC subtypes. As mentioned before, there is still a debate on how to classify MBCs [10]. Basically it is classified as mesenchymal or epithelial; we aim to compare mesenchymal subtype with other subtypes.

5. Conclusion

In summary, this study is one of the few studies about the survival outcomes of subtypes of MBCs. Nonetheless, it is the only study demonstrating that mesenchymal subtype had the worse survival outcomes. Since there are

still controversial findings between our study and recently published study [10], a unified pathologic classification and further studies are needed to determine the outcome of different subtypes of MBCs in larger series.

Declarations

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Conflict of Interest: The authors declare that they have no conflict of interest.

Submission declaration and verification: The work described has not been published previously. It is not under consideration for publication elsewhere. Its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of informed consent: Informed consent was obtained from all individual participants included in the study as a part of routine surgical procedures. Surgical and interventional treatment procedures were compliant with up-to-date and standard of care treatment modalities.

Ethics approval: This is an observational study. The Istanbul University Istanbul Faculty of Medicine Research Ethics Committee has confirmed that no ethical approval is required for this retrospective study.

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