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## Abstract

**Introduction:** Metaplastic breast cancer (MBC) is a rare pathological type with an incidence rate of not more than 1%, and has been reported to be often detected after its progression and highly malignant with a high proportion of triple negative type tumors, with poor outcomes as compared to IDC [1] [2] [3]. We analyzed clinicopathological characteristics of patients who underwent surgery for epithelial MBC at our department. **Patients and Methods:** From January 2000 to March 2014, a total of 2120 patients underwent surgery for breast cancer, and MBC was diagnosed in 15 of these patients. Fourteen of the 15 had epithelial MBC and were included in this study. The present study compared clinicopathological characteristics of MBC with those of IDC of triple negative type (TN type group) and IDC of non-triple negative type (IDC group). **Results:** Breast conserving surgery was performed in 7 patients with MBC (50%), a proportion clearly lower than the 64.3% in the IDC group. The mean tumor size was 3.8 cm, which was greater than the 2.13 cm in the TN type group and the 1.7 cm in the IDC group. About nuclear grade, the proportion of grade III was 57.1%, markedly higher than the 38.6% in the TN type group and the 12.6% in the IDC group. All patients were estrogen receptor (ER) and progesterone receptor (PgR) negative; 11 patients were TN type tumors and 3 were HER2 type. **Conclusion:** We studied patients who underwent surgery for epithelial MBC. The examined cases showed clinicopathological characteristics of the disease, including large tumors with a highly malignant nature at the initial detection, higher Ki-67 levels, ER and PgR negativity (all cases), mostly TN type, and a high recurrence rate.

## Keywords

Breast Cancer, Metaplastic Breast Cancer, Triple Negative Type, Epithelial-Mesenchymal Transition

## 1. Introduction

Metaplastic breast cancer (MBC), a special form of breast cancer, refers to a group of various invasive ductal carcinomas (IDC) having a phenotype of either non-glandular epithelium or a mix of non-glandular epithelium and mesenchymal stem cells. MBC is a rare tissue type with an incidence rate of not more than 1%, and has been reported to be often detected after its progression and highly malignant with a high proportion of triple negative type tumors, with poor outcomes as compared to IDC [1] [2] [3]. MBC has recently attracted considerable attention from the perspectives of the epithelial-mesenchymal transition (EMT) concept, molecular pathology studies, and targeted therapy development [4] [5]. We herein analyzed clinicopathological characteristics of patients who underwent surgery for epithelial MBC at our department.

## 2. Patients and Methods

From January 2000 to March 2014, a total of 2120 patients underwent surgery for breast cancer, and MBC was diagnosed in 15 of these patients. In this study, epithelial MBC was applied and mesenchymal MBC was excluded. Fourteen of the 15 (0.67%) had epithelial MBC and were included in this study. All patients were female with a mean age of 52.9 years (range: 33 to 74 years), younger than the mean age of 56.9 years in IDC patients. Two patients who had been diagnosed with IDC of non-special type (NS type) based on preoperative core needle biopsy received primary systemic therapy (PST). There was no difference in the background factors in each group. The present study compared clinicopathological characteristics of MBC with those of IDC of triple negative type (TN type group) and IDC of non-triple negative type (IDC group). This study was conducted in compliance with the Declaration of Helsinki.

## 3. Results

The background factor of the patient was shown in **Table 1**, and the clinicopathological examination of MBC with those of IDC of triple negative type (TN type group) and IDC of non-triple negative type (IDC group) was shown in **Table 2**. 1) Stage, operative procedure, and tissue type: The stage classification of cancer was I in 5 patients and II or higher in 9 patients (64.2%). In the IDC group, stage II and higher accounted for 39.3%, indicating a higher proportion of advanced cancer cases among those with MBC (**Figure 1**). Breast conserving surgery was performed in 7 patients with MBC (50%), a proportion clearly lower than the 64.3% in the IDC group. The tissue type classification was squamous cell carcinoma in 7 patients, adenosquamous carcinoma in 4, spindle cell carcinoma in 2, and squamous cell carcinoma + spindle cell carcinoma in one. 2) Oncological characteristics: The mean tumor size was 3.8 cm (range: 0.4 to 9.0 cm), which was greater than the 2.13 cm in the TN type group and the 1.7 cm in the IDC group. Only 1 patient had lymph node metastasis. The degree of nuclear atypia was grade I in 2 patients, grade II in 4, and grade III in 8; the proportion of grade III was 57.1%, markedly higher than the 38.6% in the TN type group and the 12.6% in the IDC group (**Figure 2**). The mean Ki-67 level was 55.4%, similar to the 53.5% in the TN type group

**Table 1.** Case of epithelial metaplastic carcinoma.

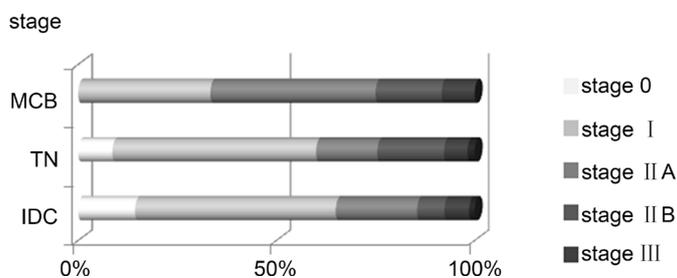
N0	Age	Pathology	Stage	Size*	Grade	ER	PgR	HER3
1	46	SCC	2a	22	II	-	-	1+
2	53	SCC	2a	32	III	-	-	3+
3	58	SCC	1	9	II	-	-	3+
4	55	SCC	1	17	II	-	-	-
5	64	SCC	2a	29	II	-	-	-
6	33	Adenosquamous ca	1	4	I	-	-	-
7	54	Spindle cell ca	1	20	III	-	-	-
8	55	Adenosquamous ca	2b	70	III	-	-	-
9	54	Adenoaquamous ca	2a	25	III	-	-	-
10	75	Adenosquamous ca	2a	25	III	-	-	3+
11	41	Spindle cell ca	2b	44	III	-	-	3+
12	42	SCC	3b	90	III	-	-	-
13	42	SCC+ spindle cell ca	2a	28	II	-	-	1+
14	69	SCC	1	90	III	-	-	-

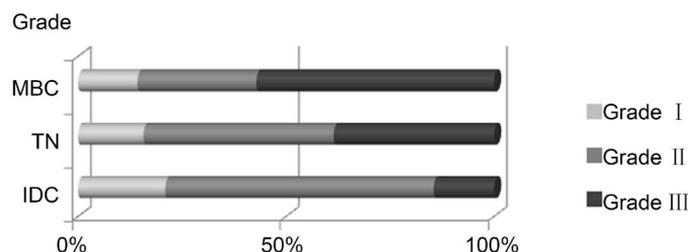
SCC: Squamous cell carcinoma, ER: estrogen receptor PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2, \* size: tumor size (mm).

**Table 2.** Clinicopathological characteristics of metaplastic breast cancer and invasive ductal carcinoma (non TN type and TN type).

	Metaplastic ca	IDC(TN type)	IDC(non TN type)
Tumor size (average value)	3.2 cm	2.1 cm	1.7 cm
Grade III	58.3%*	69.6%*	12.6%
Ki-67	53.8%*	53.3%*	24.2%
Ly(+)	16.7%	19.8%	13.5%
V(+)	25.0%	13.7%	10.5%
Breast conserving surgery	50.0%	62.3%	64.3%
Recurrence rate	14.3%	8.3%	9.2%

\*p ≤ 0.05.

**Figure 1.** Pathological staging of metaplastic breast cancer and other control group.



**Figure 2.** Nuclear grade of metaplastic breast cancer and other control group.

but significantly higher than the 24.2% in the IDC group. Vascular invasion parameters showed no significant differences; *ly*(+) was 16.7% versus 19.8% in the TN type group and 13.5% in the IDC group; *v*(+) was 25.0% versus 13.7% in the TN type group and 10.5% in the IDC group. In the 2 patients given pre-operative PST, chemotherapy response was determined to be grade 1a in both. 3) Biological characteristics: All patients were estrogen receptor (ER) and progesterone receptor (PgR) negative; 11 patients were classified as having TN type tumors and 3 as having HER2 type. 4) Postoperative adjuvantive therapy and outcome: No postoperative therapy was administered to 2 patients who declined treatment, and standard therapy with anthracycline or taxane was administered according to established guidelines to all other patients, in the same manner as for IDC. Local recurrence was reported 7 years post-surgery in 1 patient who had undergone breast conserving surgery for squamous cell carcinoma. This patient had rejected postoperative pharmacotherapy and received radiotherapy and was under follow-up observation alone. After the recurrence, this patient underwent mastectomy and is currently being treated. Another patient experienced bone metastasis but none of the 14 patients have died, to date. The recurrence rate of 14.3% with MBC is higher than the 9.2% in the TN type group and the 8.3% in the IDC group.

#### 4. Discussion

MBC is a rare tissue type with an incidence of approximately 1%. The WHO classification categorizes MBC into two groups: tissue morphology of pure epithelium (epithelial type) and a mixture of epithelial tissue with mesenchymal tumor cells (mixed type). The epithelial MBC can be squamous cell carcinoma, adenosquamous carcinoma, spindle cell carcinoma, mucoepidermoid carcinoma, etc. On the other hand, mixed type MBC, which was not the target of the present study, may be carcinoma with bony and cartilaginous metaplasia, matrix-producing carcinoma, or carcinosarcoma. MBC reportedly has a poor outcome due to large tumor size and rapid growth [1] [2] [3].

Relevant oncological factors include not only tumor size and lymph node metastasis, but also the malignancy of the tumor, as indicated by nuclear atypia (grade), the proliferation marker Ki-67, and vascular invasion parameters (*ly* and *v* factors). Large tumors are characteristic of MBC, and the present study indicated the size of MBC to exceed that of IDC. The grade distribution was generally similar to that of TN type, but MBC had a higher proportion of grade III and a higher frequency of vascular invasion.

With respect to the greater malignancy and tumor size, the rate of lymph node metastasis was low (only 1 patient), which appears to be a key feature of MBC. Poor prognostic factors for this tissue type include a tumor size of 4.0 cm or greater, cutaneous invasion, and lymph node metastasis. In the present study, outcomes were generally good with only 1 case each of local recurrence and distant metastasis and no case of death.

Regarding biological factors, most patients were negative for hormone receptors and HER2, although some had HER2-positive cancer. Characteristics similar to those of TN type have been reported [6] [7]. Therefore, hormone therapy and molecular targeted therapy are not feasible and chemotherapy is the only option for postoperative adjunctive therapy. At the present time, no MBC-specific pharmacotherapy is available, and anthracyclines and taxanes are usually used based on the therapeutic strategy for IDC. Currently, expectations are rising for the use of bevacizumab, which can be administered for breast cancer, and molecular targeted agents, such as cetuximab which is used for EGFR-positive colorectal cancer [1].

The concept of EMT is also attracting attention in the field of cancer research. Tumor growth factor (TGF)  $\beta$  and E-cadherin are among the representative molecules involved in EMT. Particularly in triple negative breast cancer, overexpressions of EMT-associated genes (e.g., TWIST1 and SNAIL1) are significantly higher than in other tumor types, and these genes are known to regulate the expression of E-cadherin [8] [9]. Lower expression of E-cadherin is associated with partial EMT, and future studies elucidating the pathology of metaplastic cancer may lead to the discovery of new target molecules.

## 5. Conclusion

We studied patients who underwent surgery for epithelial MBC. The examined cases showed clinopathological characteristics of the disease, including large tumors with a highly malignant nature at the initial detection, higher Ki-67 levels, ER and PgR negativity (all cases), mostly TN type, and a high recurrence rate. As elucidation of the pathology of metaplastic cancer is likely to lead to the discovery of new target molecules involved in EMT, the accumulation of case studies of MBC and other metaplastic tumors is necessary.

## Consent

Informed consent was obtained from each patient for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Conflict of Interests

The authors declare that they have no conflict of interests.

## Acknowledgements

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