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Review

Metaplastic carcinoma of the breast: A case series and review of the literature

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ABSTRACT

Purpose: Metaplastic breast carcinoma (MBC) is a rare aggressive type of breast cancer, which accounts for less than 1% of breast tumors. Since its recognition as a distinct pathological entity in 2000, number of MBC patients has been increasing over years. We aimed to report a series of 7 cases of MBC treated in our clinics.

Materials and methods: Between 2006 and 2015, 7 cases with diagnosis of MBC were retrospectively reviewed. Patients' characteristics, clinicopathological features and types of surgery were evaluated.

Results: All patients were female with a median age of 51(40–65) years. Median tumor size was 40 mm (35–85 mm). Two patients had breast-conserving surgery and 4 patients had mastectomy. One patient received chemotherapy due to extensive metastatic disease at the time of presentation. Only one patient had one positive sentinel lymph node with no other involvement in the non-sentinel nodes. Two patients had spindle cell carcinoma, 2 patients had pure epithelial type, and 3 patients had mixed epithelial and mesenchymal type MBC. Most common component of MBC was squamous cell metaplasia that was found in 4 out of 7 patients. Six patients had triple negative tumors except the patient with disseminated disease. This patient had estrogen receptor positive, progesterone receptor negative tumor with human epithelial receptor-2 (HER2) over-expression. Median Ki67 score measured in 5 patients was 57% (40–95%).

Conclusion: Our small series is consistent with the literature. MBC rarely metastasize to axillary lymph nodes despite large size and are usually triple negative with high Ki-67 scores indicating aggressiveness and lack of response to hormonal therapy. Larger series of patients are needed to find and test new biomarkers to develop potential targeted therapy for subgroups of the disease.

1. Introduction

Metaplastic breast carcinoma (MBC) was not formerly recognized as a distinct pathologic entity until 2000 when it was classified by World Health Organization (WHO).[1] Despite increased recognition of this specific histologic subtype, the reported incidence still remains under 1% of all breast malignancies.[2–6]

Aggressive biological parameters like high histological grade are more frequently found in MBC compared to invasive ductal carcinoma of breast, which drives a more aggressive treatment.[4] Mastectomy rates are higher due to large tumor size at the time of presentation despite lower incidence of axillary lymph node involvement.[2,7,8]

MBC typically do not express estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2), which is suggested to be a reflection of absence of extensive glandular component by Mourad et al.[9] These tumors are considered as a subgroup of basal like breast cancers when classified by gene expression[10–13] and carry poor prognosis due to lack of response to hormonal therapy as shown by previous reports.[3,14–17]

In the present study, we report seven patients with metaplastic breast carcinoma who were treated in a single institution and discuss the clinicopathological features and treatment strategies.

2. Materials & method

Files of the patients who were operated between January 2006 and March 2015 were retrieved from the hospital database. Seven cases of MBC were identified. The patients' age, gender, tumor size,

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histologic grade, subgroups of MBC, ER, PR, HER2 expression, Ki67 scores, additional immunohistochemical staining (if present), types of surgical procedure, axillary status were noted from definitive pathology reports. Adjuvant and induction treatment strategies were collected from hospital files.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) program, version 15.0 (SPSS Inc., Chicago, IL, USA). Age and tumor size were expressed as medians.

3. Results

All patients were female with a median age of 51 (40–65) years. The common presenting symptom was palpable mass in the breast. Median tumor size was 40 mm (35–85 mm). Two patients had breast-conserving surgery and 4 patients had mastectomy. One patient did not undergo surgery and received chemotherapy due to extensive metastatic disease at the time of presentation. Only one patient had one positive sentinel lymph node with no other involvement in the non-sentinel nodes. Axillary dissection was performed in one patient without sentinel lymph node biopsy because of clinically palpable lymph nodes but definitive pathology revealed no metastases. Two patients had pure epithelial type, 2 patients had spindle cell carcinoma and 3 patients had mixed epithelial and mesenchymal type MBC. Most common component of MBC was squamous cell metaplasia that was found in 4 out of 7 patients. Six patients had triple negative tumors except the patient with disseminated disease. This patient had estrogen receptor positive, progesterone receptor negative tumor with HER2 overexpression. Median Ki67 score measured in 5 patients was 57% (40–95%). Epidermal growth factor receptor (EGFR) and CK5/6 were studied at discretion of the pathologist in three patients and overexpression was found in these patients.

4. Discussion

Metaplastic breast carcinoma is a rarely seen neoplasm, which constitutes less than 1% of all malignant breast tumors.[2–6] The patients with MBC constitute 0.62% of patients with breast cancer in our series and is consistent with the literature.[2–6]

This rare tumor is composed of a mixed group of neoplasms containing both glandular and non-glandular patterns with epithelial and/or mesenchymal components.[1] Epithelial type of MBC is further classified into (1) squamous cell carcinoma, (2) adenocarcinoma with spindle cell differentiation, (3) adenosquamous carcinoma, whereas mixed type of MBC is classified into (1) carcinoma with chondroid metaplasia, (2) carcinoma with osseous metaplasia, and (3) carcinosarcoma.[1] Wargotz et al has classified MBC into five types according to cytopathological features which are (1) spindle cell, (2) squamous cell, (3) matrix-producing, (4) carcinosarcoma, and (5) MCB with osteoclastic giant cells.[18–22] Oberman et al defined subgroups as spindle cell carcinoma, invasive ductal carcinoma with extensive squamous metaplasia and invasive carcinoma with pseudosarcomatous metaplasia and he concluded that pathologic subclassification had no clinical significance due to lack of correlation between microscopic pattern and prognosis.[23] Tse et al classified MBC into three groups as (1) epithelial only carcinoma, (2) biphasic epithelial and sarcomatoid carcinoma and (3) monophasic spindle cell carcinoma.[24] The prognoses of each of these groups varied widely and it was suggested to lead to problems in clinical practice.[24] The varying classification of MBC further complicates the information in existing studies, which are already limited in number due to rarity of this tumor.[23–25]

When we classified the tumors in our series according to WHO 2 patients had pure epithelial type MBC (Fig. 1) and 2 patients had

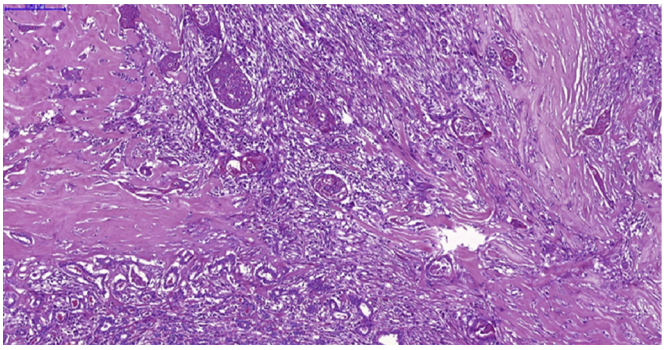

Fig. 1. Metaplastic squamous cell carcinoma H&E. Both glandular and squamous differentiation is present

spindle cell carcinoma (Fig. 2) whereas 3 patients had mixed epithelial and mesenchymal type (Fig. 3). Most common component of the tumors was squamous cell metaplasia, which was found in 4 patients. Spindle cell carcinoma was reported to be the most common type in western countries[8] and China[26] whereas squamous cell carcinoma was the most common type in Hong Kong, Singapore and Taiwan.[27] The different frequencies of distinct subtypes in different populations might have resulted from small number of patients in most studies and variation in classification.[6,26]

Metaplastic breast carcinoma usually affects females over 50 years old.[1,3,4,6] In our series all patients were female and the median age was 51 years (40–65). They presented with lump in the breast and the median tumor size was 40 mm (35–85 mm). This is typical of MBC in which tumor size at presentation is frequently larger than 3 cm.[4,27] Large tumor size is suggested to be a result of rapid growth rate due to poorly differentiated or undifferentiated tumors compared to invasive ductal carcinoma which has a relatively long preclinical phase that allows early detection by mammography.[4] Only 29.5% of MBC were found to be <2 cm in size compared with 65.2% of invasive ductal carcinoma in a study by Pezzi et al.[4]

Larger size of MBC probably leads to increased rates of mastectomy. According to Surveillance, Epidemiology and End Results (SEER) database total mastectomy were used more frequently in MBC than in invasive ductal carcinoma.[28] Breast conserving surgery and adjuvant radiotherapy were reserved for small sized tumors. However, when corrected for tumor size rates of breast conserving surgery and mastectomy were similar between MBC and other tumors, suggesting that the principles for breast cancer surgery have been applied to patients with MBC.[4] In our series, only two patients had breast-conserving surgery and four patients had mastectomy. Larger tumor size also explains the higher stage of

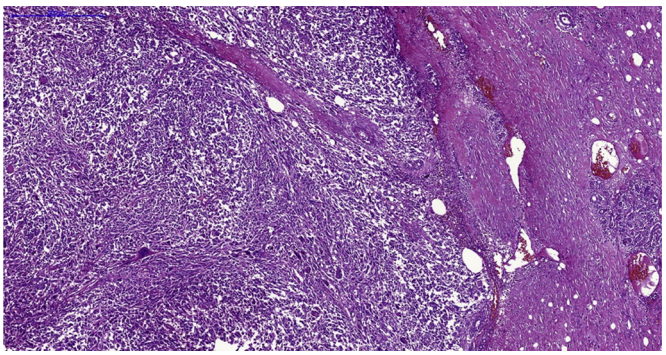

Fig. 2. Metaplastic spindle cell carcinoma H&E. The tumor is composed of atypical spindle cells

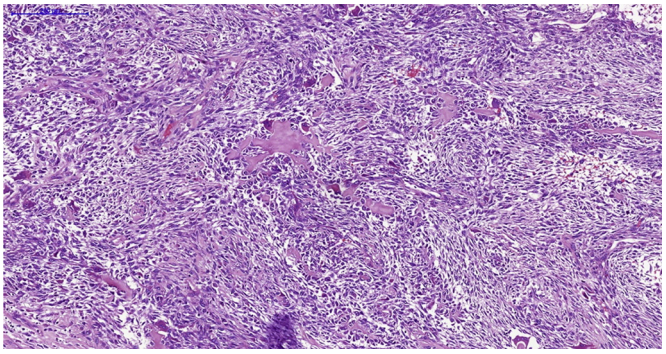

Fig. 3. Mixed epithelial and mesenchymal type metaplastic carcinoma. H&E. Osseous differentiation is present

these tumors compared to invasive ductal tumors which leads to increased frequency of treatment with systemic chemotherapy which is also justified by higher tumor grade and negative hormone receptor status.[4,6]

Five patients underwent sentinel lymph node biopsy and only one patient was found to have one positive sentinel lymph node for metastasis with no other involvement in the non-sentinel nodes. The metastasis recorded in the sentinel lymph node was due to ductal carcinoma component. Axillary dissection without sentinel node biopsy was performed in one patient with clinically palpable lymph nodes in the axilla but revealed no metastases. These findings are concordant with the previous studies which reported that MBC was associated with low incidence of axillary metastasis despite large tumor size and high histologic grade.[17,27,29,30] The paucity of nodal involvement was attributed to the presence of sarcomatous elements[4] and Huvos et al reported that the squamous subtype had a higher incidence of axillary nodal spread.[31] Hypothetically, axillary surgery may be questioned in patients with preoperative diagnosis of MBC, but in reality preoperative diagnosis of this particular tumor with needle biopsy is inconclusive due to large size and tumor heterogeneity, which entails excisional biopsy for definitive diagnosis.[26,32] Despite low rates of axillary involvement MBC has high potential for distant metastases via hematogenous route (mostly lung and bone).[3–5,7,33,34]

There is limited data about the response to induction chemotherapy.[3,17,35] In a study by Chen et al, 12 patients received chemotherapy due to metastatic disease and only two patients showed partial response whereas 10 patients experienced disease progression.[35] In this study, three of 17 patients who received chemotherapy due to MBC showed partial response to taxane-based chemotherapy whereas none of the patients responded to anthracycline, vinorelbine or cyclophosphamide based regimens. One patient in our series received taxane based chemotherapy plus trastuzumab due to extensive metastatic disease at the time of diagnosis and she died due to disease progression after 17 months. This patient had invasive ductal carcinoma with squamous metaplasia and the tumor was estrogen receptor positive, progesterone receptor negative with HER2 over-expression. HER2 over-expression is rarely observed in MBC. Only one patient in a 26 patients series was reported to have adenosquamous carcinoma with HER2 overexpression.[5]

Metaplastic breast carcinoma (>90%) displays triple negative phenotype, preferentially has a basal-like or claudin-low molecular subtype and frequently harbors mutations in the TP53 gene.[11,12,15,36] Triple negative tumors in 6 patients were consistent with the literature. Ki67 score was measured in 5 patients and the median was 57% (40–95%). CK5/6 and EGFR were studied at discretion of the pathologist in three patients and overexpression was found. These tumors were considered as basal like. Reis-Filho et al reported that 93.8% of all MBC displayed basal like phenotype.[13] Basal like tumors are heterogeneous in their expression profile, morphology, immunophenotype, prognosis and treatment response.[37]

MBC is also enriched in markers of epithelial-mesenchymal transition and cancer stem cells.[38–41] Epithelial-mesenchymal transition is a process by which cells of epithelial origin lose epithelial characteristics and acquire a mesenchymal phenotype with increased migratory behavior, tumor invasion and progression.[42,43] Possible links of induction of epithelial mesenchymal transition and gain of cancer stem cell properties[44,45] pose double jeopardy for the patient by means of chemotherapy resistant cells capable of dedifferentiation and propensity for invasion.[38] Overexpression of epithelial-mesenchymal transition inducers like vimentin and SPARC were found to be associated with higher grade and triple negative status in MBC.[46] Tumors with positive basal marker and cancer stem cell expression are independent indicators for poor prognosis.[35,40,47]

Despite potentially specific characteristics, MBC have been treated in the similar pattern with invasive ductal carcinoma, because it has been suggested not to alter prognosis.[48–50] However, the disease-free and overall survival of patients with MBC have been found to be worse compared to invasive ductal carcinoma despite few controversial reports.[28,51,52] In a review by Toumi et al 5-year disease-free survival ranged between 42% and 84% and 5-year overall survival ranged from 64% to 83%.[7] There is a possibility that MBC patients might not receive the optimal loco-regional and systemic treatment, because the adjuvant treatment and/or regimen of invasive breast cancer has largely based on pT and pN stage.[2]

In our series, 5 patients except one received adjuvant radiation treatment and chemotherapy as suggested by the tumor board after surgery. The beneficial effect of adjuvant radiation therapy in breast conserving surgery and total mastectomy has been repeatedly reported although there remains some controversial issues.[28,51–54] This might be the reason why choice of the surgical procedure has been reported to affect outcome since most of the patients with breast conserving surgery receive adjuvant radiation therapy.[33] As reported in KROG 13-07 study, the loco-regional recurrences mostly occurred out of the radiation field despite low incidence of nodal involvement. The authors have suggested breast conserving surgery plus radiation therapy should be the first choice for small tumors and the modification of radiation treatment indication and/or adequate field was needed in MBC in contrast to other invasive breast cancers.[2]

So far the attempts to find prognostic markers of MBC have been inconclusive. Lee et al[33] have reported that squamous type was more aggressive than the non-squamous whereas sarcomatoid type has been found to be more aggressive than other triple negative cancers by Lester et al.[54] Spindle cell carcinoma has been suggested to be associated with worse prognosis by Rakha et al,[8] in contrast to a large population based study by Zhang et al[26] which has reported that spindle cell carcinoma was not associated with decreased disease free or overall survival despite it was found to be the most frequent subtype in Chinese population. Yamaguchi et al reported that the presence of high-grade spindle cells was at least one important prognostic factor and was not associated with tumor size and lymph node metastases. Additionally, sarcomatous change of squamous cells was found to be high grade and exhibited a high recurrence rate and metastases.[55] Others also supported that sarcomatoid breast tumors had sarcomatoid behavior.[56,57]

Among parameters found to be associated with poor prognosis there have been lymph node stage, lymphovascular invasion and high Ki67 scores.[8,32,34] In a recent study by Okada et al who

compared 46 cases of MBC with invasive ductal and lobular carcinoma, it was reported that presence of skin invasion and age not exceeding 39 years significantly increased the hazards ratio for tumor recurrence and tumor death, whereas the squamous cell carcinoma in the lymph nodes significantly increased the hazards ratio for tumor death.[52]

Some immunohistochemical characteristics like EGFR overexpression, EGFR gene amplification, focal staining of CK14 have been reported to be associated with decreased disease free survival.[26,58] Although most of MBC display triple negative phenotype, there is a subtype that is hormone receptor(s) and/or HER2 positive. However, it seems to be there is no statistically significant difference in three-year disease-free survival between non-triple negative and triple negative MBC.[59] Nevertheless, irrespective of the receptor status there is subgroup of MBC with better prognosis like low grade adenosquamous and fibromatosis like subtypes.[27] It is likely we are dealing with two subsets of tumors - one with early relapse and aggressive clinical course and the other one with a more favorable prognosis despite traditional adverse biological features.[7,16,58–60] For the time being, we do not have reliable parameters to differentiate between these two types.

5. Conclusion

Our present knowledge of MBC is limited. The rarity and the heterogeneity of MBC in biological and morphological features as well as different classification and treatment strategies in the literature have foiled the attempts to retain satisfying data and evidence to establish a solid treatment strategy in this unwonted breast neoplasm. Although promising results in small and selected group of patients who were treated according to cancer stem cell characteristics are encouraging, more effort should be exerted to find potential molecular targets and more trials should be conducted to pass beyond small series and to test the efficiency of targeted therapies.[61]

Conflict of interest

The authors have no conflict of interest to imply.

References

1. Tavassoli DA, Devilee P, eds. *World Health Organization: Tumors of the Breast and Female Genital Organs*. Oxfordshire: Oxford University; 2003.
2. Yu JI, Choi DH, Huh SJ, et al. Unique characteristics and failure patterns of metaplastic breast cancer in contrast to invasive ductal carcinoma: A retrospective multicenter case-control study (KROG 13-7). *Clin Breast Cancer*. 2015;15(2):105–115.
3. Luini A, Aguilar M, Gatti G, et al. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: The experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat*. 2007;101:349–353.
4. Pezzi MC, Lina PP, Karin C, et al. Characteristics and treatment of metaplastic breast cancer: Analysis of 892 cases from the National Cancer Data Base. *Ann Surg Oncol*. 2007;14:166–173.
5. Barnes PJ, Boutilier R, Chiasson D, Rayson D. Metaplastic breast carcinoma: Clinical-pathological characteristics and HER2/neu expression. *Breast Cancer Res Treat*. 2005;91(2):173–178.
6. Schwartz TL, Mogal H, Papageorgiou C, Veerapong J, Hsueh EC. Metaplastic breast cancer: Histologic characteristics, prognostic factors and systemic treatment strategies. *Exp Hematol Oncol*. 2013;2:31–36.
7. Toumi Z, Bullen C, Tang ACS, Dalal N, Ellenbogen S. Metaplastic breast carcinoma: A case report and systematic review of the literature. *Pathol Int*. 2011;61:582–588.
8. Rakha EA, Tan PH, Varga Z, et al. Prognostic factors in metaplastic carcinomas of the breast: A multi-institutional study. *Br J Cancer*. 2015;112:283–289.
9. Mourad WA. Book review: Rosen's breast pathology. *Ann Saudi Med*. 1998;18:278.
10. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406:747–752.
11. Weigelt B, Kreike B, Reis-Filho JS. Metaplastic breast carcinomas are basal-like breast cancers: A genomic profiling analysis. *Breast Cancer Res Treat*. 2009;117:273–280.
12. Weigelt B, Geyerb FC, Reis-Filhob JS. Histological types of breast cancer: How special are they? *Mol Oncol*. 2010;4:192–208.
13. Reis-Filho JS, Milanezi F, Steele D, et al. Metaplastic breast carcinomas are basal like tumours. *Histopathology*. 2006;49:10–21.
14. Hennesy BT, Gonzales-Angulo AM, Stemke-Hale K, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. *Cancer Res*. 2009;69:4116–4124.
15. Hennesy BT, Giordiano S, Broglio K, et al. Biphasic metaplastic sarcomatoid carcinoma of the breast. *Ann Oncol*. 2006;17:606–613.
16. Jung SY, Kim HY, Nam BH, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. *Breast Cancer Res Treat*. 2010;120:627–637.
17. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: Prognosis and response to systemic therapy. *Ann Oncol*. 1999;10(4):413–419.
18. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. I Matrix producing carcinoma. *Hum Pathol*. 1989;20:628–635.
19. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. II: Spindle cell carcinoma. *Hum Pathol*. 1989;20:732–740.
20. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast III Carcinosarcoma. *Cancer*. 1989;64:1490–1499.
21. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. IV: Squamous cell carcinoma of ductal origin. *Cancer*. 1990;65:272–276.
22. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. V: Metaplastic carcinoma with osteoclastic giant cells. *Hum Pathol*. 1990;21:1142–1150.
23. Oberman HA. Metaplastic carcinoma of the breast. A clinicopathologic study of 29 patients. *Am J Surg Pathol*. 1987;11:918–929.
24. Tse GM, Tan PH, Putti TC, Lui PCW, Chaiwun B, Law BKB. Metaplastic carcinoma of the breast: A clinicopathological review. *J Clin Pathol*. 2006;59:1079–1083.
25. Yamaguchi R, Rie H, Maeda I, et al. Clinicopathologic study of 53 metaplastic carcinomas: Their elements and prognostic implications. *Hum Pathol*. 2010;41:679–685.
26. Zhang Y, Lv F, Yang Y, et al. Clinicopathological features and prognosis of metaplastic breast carcinoma: Experience of a major Chinese cancer center. *Plos One*. 2015;10(6):e0131409. http://dx.doi.org/10.1371/journal.pone.0131409. eCollection 2015.
27. Lai HW, Tseng LM, Chang TW, et al. The prognostic significance of metaplastic carcinoma of the breast (MCB) – A case controlled comparison study with infiltrating ductal carcinoma. *Breast*. 2013;22:968–973.
28. Nelson RA, Guye ML, Luu T, Lai LL. Survival outcomes of metaplastic breast cancer patients: Results from a US population-based analysis. *Ann Surg Oncol*. 2015;22(1):24–31.
29. Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. *Acta Oncol*. 2006;45(2):188–195.
30. Beatty JD, Atwood M, Tickman R, Reiner M. Metaplastic breast cancer: Clinical significance. *Am J Surg*. 2006;191(5):657–664.
31. Huvos AG, Lucas JCJ, Foote FWJ. Metaplastic breast carcinoma. Rare form of mammary cancer. *N Y State J Med*. 1973:1078–1082.
32. Park HS, Park S, Kim JH, et al. Clinicopathologic features and outcomes of metaplastic breast carcinoma: Comparison with invasive ductal carcinoma of the breast. *Yonsei Med J*. 2010;51(6):864–869.
33. Lee H, Jung SY, Ro JY, et al. Metaplastic breast cancer: Clinicopathological features and its prognosis. *J Clin Pathol*. 2012;65(5):441–446.
34. Song Y, Liu X, Zhang G, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. *World J Surg Oncol*. 2013;11:129–138.
35. Chen IC, Lin CH, Huang CS, et al. Lack of efficacy to systemic chemotherapy for treatment of metaplastic carcinoma of the breast in the modern era. *Breast Cancer Res Treat*. 2011;130:345–351.
36. Lien HC, Lin CW, Mao TL, Kuo SH, Hsiao CH, Huang CS. p53 overexpression and mutation in metaplastic carcinoma of the breast: Genetic evidence for a monoclonal origin of both the carcinomatous and the heterogeneous sarcomatous components. *J Pathol*. 2004;204:131–139.
37. TC1 Chao, Wang CS, Chen SC, Chen MF. Metaplastic carcinomas of the breast. *J Surg Oncol*. 1999;71:220–225.
38. Oon ML, Thike AA, San TY, Tan PH. Cancer stem cell and epithelial-mesenchymal transition markers predict worse outcome in metaplastic carcinoma of the breast. *Breast Cancer Res Treat*. 2015;150:31–41.
39. Tan EY, Thike AA, Breast Surgical Team at Outram, Tan PH. ALDH1 expression is enriched in breast cancers arising in young women but does not predict outcome. *Br J Cancer*. 2013;109:109–113.
40. Lee HE, Kim JH, Kim YJ, et al. An increase in cancer stem cell population after primary systemic therapy is a poor prognostic factor in breast cancer. *Br J Cancer*. 2011;104:1730–1738.
41. Abraham B, Fritz P, McClellan M, et al. Prevalence of CD44+/CD24-/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. *Clin Cancer Res*. 2005;11:1154–1159.
42. Sarrio D, Rodriguez-Pinilla SM, Hardisson D, et al. Epithelial-mesenchymal transition in breast cancer relates to the basal-like phenotype. *Cancer Res*. 2008;68:989–997.
43. Choi Y, Lee HJ, Jang MH, et al. Epithelial-mesenchymla transition increases during the progression of in situ to invasive basal-like breast cancer. *Hum Pathol*. 2013;44:2581–2589.

44. Creighton C, Chang J, Rosen J. Epithelial-mesenchymal transition (EMT) in tumor-initiating cells and its clinical implications in breast cancer. *J Mammary Gland Biol Neoplasia*. 2010;15:253–260.
45. Mani SA, Guo W, Liao MJ, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell*. 2008;133:704–715.
46. Lien HC, Hsiao YH, Lin YS, et al. Molecular signatures of the metaplastic carcinoma of the breast by large-scale transcriptional profiling: Identification of genes potentially related to epithelial-mesenchymal transition. *Oncogene*. 2007;26:7859–7871.
47. Tsang JS, Huang YH, Luo MH, et al. Cancer stem cell markers are associated with adverse biomarker profiles and molecular subtypes of breast cancer. *Breast Cancer Res Treat*. 2012;136:407–417.
48. Harnett A, Smallwood J, Titshall V, et al. Diagnosis and treatment of early breast cancer, including locally advanced disease-summary of NICE guidance. *BMJ*. 2009;338:b438.
49. Cadoo KA, McArdle O, O'Shea AM, et al. Management of unusual biological types of breast cancer. *Oncologist*. 2012;17:135–145.
50. Theriault RL, Carlson RW, Allred C, et al. Breast cancer, version 3.2013: Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2013;11:753–761.
51. Wright GP, Davis AT, Koehler TJ, Melnik MK, Chung MH. Hormone receptor status does not affect prognosis in metaplastic breast cancer: A population-based analysis with comparison to infiltrating ductal ad lobular carcinomas. *Ann Surg Oncol*. 2014;21:3497–3503.
52. Okada N, Hasebe T, Iwasaki M, et al. Metaplastic carcinoma of the breast. *Hum Pathol*. 2010;41:960–970.
53. Tseng WH, Martinez SR. Metaplastic breast cancer: To radiate or not to radiate? *Ann Surg Oncol*. 2011;18:94–103.
54. Lester TR, Hunt KK, Nayeemuddin KM, et al. Metaplastic sarcomatoid carcinoma of the breast appears more aggressive than other triple receptor-negative breast cancers. *Breast Cancer Res Treat*. 2012;131:41–48.
55. Yamaguchi R, Horii R, Maeda I, et al. Clinicopathologic study of 53 metaplastic carcinomas: Their elements and prognostic implications. *Hum Pathol*. 2010;41:679–685.
56. Carter MR, Hornick JL, Lester S, et al. Spindle cell (sarcomatoid) carcinoma of the breast: A clinicopathologic and immunohistochemical analysis of 29 cases. *Am J Surg Pathol*. 2006;30:300–309.
57. Davis WG, Hennesy B, Babiera G, et al. Metaplastic sarcomatoid carcinoma of the breast with absent or minimal overt invasive carcinomatous component: A misnomer. *Am J Surg Pathol*. 2005;29:1456–1463.
58. Fulford LG, Reis-Filho JS, Ryder K, et al. Basal-like grade III invasive ductal carcinoma of the breast: Patterns of metastasis and long-term survival. *Breast Cancer Res*. 2007;9(1):R4. http://dx.doi.org/10.1186/bcr1636.
59. Lim KH, Oh DY, Chie EK, et al. Metaplastic breast carcinoma: Clinicopathologic features and prognostic value of triple negativity. *Jap J Clin Oncol*. 2006;64:771–775.
60. Bae SY, Lee SK, Koo MY, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. *Breast Cancer Res Treat*. 2011;126:471–478.
61. Moulder S, Moroney J, Helgason T, et al. Responses to liposomal doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: Biologic rationale and implications for stem-cell research in breast cancer. *J Clin Oncol*. 2011;29(19):572–575.