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Keywords: breast cancer; metaplastic carcinoma; prognosis; outcome; race; tumour type; grade

Prognostic factors in metaplastic carcinoma of the breast: a multi-institutional study

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Background: Metaplastic breast carcinoma (MBC) is a rare type of breast cancer that has basal-like characteristics and is perceived to have poorer prognosis when compared with conventional no specific type/ductal carcinomas (ductal/NST). However, current data on MBC are largely derived from small case series or population-based reports. This study aimed to assess the clinicopathological features and outcome of MBC identified through an international multicentre collaboration.

Methods: A large international multicentre series of MBC (no = 405) with histological confirmation and follow-up information has been included in this study. The prognostic value of different variables and outcome has been assessed and compared with grade, nodal status and ER/HER2 receptor-matched ductal/NST breast carcinoma.

Results: The outcome of MBC diagnosed in Asian countries was more favourable than those in Western countries. The outcome of MBC is not different from matched ductal/NST carcinoma but the performance of the established prognostic variables in MBC is different. Lymph node stage, lymphovascular invasion and histologic subtype are associated with outcome but tumour size and grade are not. Chemotherapy was associated with longer survival, although this effect was limited to early-stage disease. In this study no association between radiotherapy and outcome was identified. Multivariate analysis of MBC shows that histologic subtype is an independent prognostic feature.

Conclusions: This study suggests that MBC is a heterogeneous disease. Although the outcome of MBC is not different to matched conventional ductal/NST breast carcinoma, its behaviour is dependent on the particular subtype with spindle cell carcinoma in particular has an aggressive biological behaviour. Management of patients with MBC should be based on validated prognostic variables.

Mammary parenchymal cells show a high degree of phenotypic plasticity, which is seen in both benign and malignant lesions (Smith and Taylor 1969; Spagnolo and Shilkin 1983; Kaufman *et al*, 1984; Wang *et al*, 2001; Rosen 2009; van Deurzen *et al*, 2011).

Conventional (ductal/no specific type) invasive breast carcinoma occasionally shows minor components of metaplastic elements with squamous and/or mesenchymal appearances (Kaufman *et al*, 1984). However, when the metaplastic components form a

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significant proportion (usually >10%, although some authors have used different cutoffs including <10% (Downs-Kelly *et al*, 2009), ≥20% (Gwin *et al*, 2010) or ≥50% (Yamaguchi *et al*, 2010)) the term metaplastic breast carcinoma (MBC) is used. Although MBC is rare comprising 0.3%–1.5% of breast cancer, it is recognized to be a heterogeneous group of tumours with multiple subtypes reflecting variable histological appearances (Hennessy *et al*, 2006; Tse *et al*, 2006; Pezzi *et al*, 2007; Yamaguchi *et al*, 2010; Tseng and Martinez, 2011; Reis-Filho *et al*, 2012). There is a perception that MBC is an aggressive tumour with poor outcome. This is mainly based on previous studies of MBC that included either a limited number of cases or a population-based database without histological confirmation and with different clinical stages (i.e., stage I to IV (Hennessy *et al*, 2006)) and ethnicity (Foschini *et al*, 1993; Rayson *et al*, 1999; Hennessy *et al*, 2006; Tse *et al*, 2006; Luini *et al*, 2007; Pezzi *et al*, 2007; Jung *et al*, 2010; Yamaguchi *et al*, 2010; Bae *et al*, 2011; Tseng and Martinez 2011; Lee *et al*, 2012; Lester *et al*, 2012; Reis-Filho *et al*, 2012). In addition, some molecular studies have shown some shared characteristics between MBC and the aggressive high grade basal-like class of ductal carcinoma (Reis-Filho *et al*, 2006). As a consequence, the outcome and prognostic risk stratification of patients with MBC remain uncertain. Clinicopathological variables that are well-validated in conventional invasive breast carcinoma may behave differently in MBC. Therefore, in this large international multicentre study of MBC with histological confirmation and long-term follow-up, we aimed to assess the prognostic value of the different clinicopathological variables and determine its outcome compared with grade, node and receptor matched conventional invasive ductal carcinoma of no special type.

MATERIALS AND METHODS

This study included three case series. The first series comprises MBC diagnosed at and identified from the files of six institutions in Europe including the United Kingdom (three institutions; Nottingham, Leeds and Leicester), The Netherlands, Switzerland and Spain ($n = 313$). The second series comprises MBC identified from the files of three institutions from Asia including Singapore and Hong Kong (two institutions; $n = 92$). These series consist of cases diagnosed between 1991 and 2012. Cases were reviewed by a consultant pathologist in each centre to confirm the initial diagnosis and to assess the neoplastic cell phenotype/morphology. Criteria for diagnosis of MBC were as previously published (Rosen, 2009; Reis-Filho *et al*, 2012). MBC was defined by the presence of non-glandular epithelial (squamous) or mesenchymal (spindle or matrix producing) elements associated with DCIS or conventional mammary type invasive carcinoma. In the occasional cases lacking a conventional carcinomatous element, the diagnosis was confirmed using immunohistochemical markers of epithelial differentiation. MBC histologic subtypes included the following: spindle (including sarcomatoid and pleomorphic), squamous, mixed squamous and spindle and matrix producing types (Rosen, 2009; Reis-Filho *et al*, 2012). Variables assessed and collected include tumour histological subtype, proportion of each metaplastic component, histological grade and its components (tubule formation, pleomorphism and mitotic count), degree of cellularity, presence and degree of tumour necrosis and presence, grade and extent of associated ductal carcinoma *in situ* (DCIS). Clinicopathological characteristics including tumour size, total number of lymph nodes and number of positive nodes, lymphovascular invasion, hormone receptor and HER2 status were obtained from the database whenever available. Clinical and outcome data including menopausal status, treatment performed including local (surgical and radiotherapy) and systemic therapy (endocrine

therapy and chemotherapy), development of local, regional and distant recurrence and time to events, survival status, survival time and cause of death were collected from patients' notes. Breast cancer-specific survival (BCSS) was defined as the interval between the operation and death from (or with) breast cancer, death being scored as an event, and patients who died from other causes or were still alive were censored at the time of last follow-up (Rakha, 2013). Out of the 405 MBC, 41 cases were excluded as follows: cases presented as metastatic (within 2 months of presentation; $n = 5$), recurrent ($n = 14$) or contralateral ($n = 4$) breast cancer, cases received neoadjuvant chemotherapy or conventional mammary carcinoma with ≤10% metaplastic component ($n = 18$). The clinicopathological features of the remaining 364 MBC are shown in Table 1. Complete follow-up data of MBC after exclusion of ineligible cases was available for 285 cases.

The third series is a control group ($n = 285$) of age, histological grade, lymph node stage, oestrogen receptor (ER) and HER2 status matched conventional invasive ductal/NST primary breast carcinomas identified from the well-defined Nottingham primary operable (≤5 cm) breast cancer series ($n = 1950$) that has been described in previous publications (Rakha *et al*, 2007, 2008, 2009, 2011).

This study was approved by the Nottingham Research Ethics Committee.

STATISTICAL ANALYSIS

Survival curves were produced using the Kaplan–Meier method and were compared using log rank tests. Survival rates are presented with their 95% confidence intervals. Multivariate analyses were conducted using Cox proportional hazard regression models. The clinicopathological variables were compared using contingency tables and χ^2 -tests. All comparisons were two-sided and a p -value of <0.05 was considered significant.

RESULTS

All MBC patients were female, of whom 70% had axillary clearance and 30% had lymph node (LN) sample or sentinel node biopsy. Median LN number was 9 (range 1–46). Thirty percent showed metastatic (positive) nodes that were mainly of low number (median = 2). Forty-five percent of the positive nodes contained deposits of metaplastic elements as either pure (25%) or mixed with conventional carcinomas (20%), the remainder were involved by conventional adenocarcinoma of ductal/NST type. Diagnosis of MBC was based on the presence of non-glandular (squamous and/or mesenchymal including matrix producing) differentiation associated with conventional-type carcinomatous element (<90%) that was identified in 57% of cases and/or DCIS that was identified in 42% of cases (Table 1). More mixed spindle and squamous (37%) and spindle (28%) presented at an advanced stage (pT3&4) than squamous (21%) and matrix producing (18%) carcinomas but this difference was not significant ($P = 0.17$).

Of the whole series, 276 (76%) were from Western countries and 88 (24%) from Asian countries. There was a significant difference between MBC diagnosed in Western countries and Asian countries with frequent mastectomy and higher histological grade tumours with more squamous and less spindle carcinoma subtypes in Asian countries (Table 2).

Outcome analysis. During the period of follow-up (maximum 244 months, interquartile range 56), 65 patients developed recurrent disease and 95 patients died (55 of BC and 40 of other causes). No difference in the outcome was detected between recent (at or after 2005) and old (before 2005) cases ($X^2 = 0.08$, $P = 0.779$).

Table 1. Clinicopathological features of metaplastic breast carcinoma (n = 364)

Variables	MBC
Time of diagnosis^a	
Before 2005	43%
At or after 2005	57%
Mean age in years (range)	60 (27–96)
Menopausal status	
Pre/perimenopausal	32%
Postmenopausal	68%
Type of surgery	
Breast conserving surgery	41%
Mastectomy	59%
Tumour Size	
TNM pT1	23%
TNM pT2	53%
TNM pT3&4	24%
Focality	
Localised	89%
Multifocal	11%
LN stage	
1 (LN negative)	71%
2 (1–3 positive nodes)	19%
3 (>3 positive nodes)	10%
Invasive carcinoma grade	
1	2%
2	23%
3	75%
Mitotic counts	
1	9%
2	19%
3	72%
Degree of nuclear pleomorphism	
Mild	2%
Moderate	7%
Marked	91%
Associated conventional invasive carcinoma	
Yes	57%
No	43%
Proportion of metaplastic elements	
11%–50%	32%
51%–90%	24%
> 90%	44%
Degree of cellularity	
High	59%
Intermediate	31%
Low	2%
Heterogeneous	8%
Associated DCIS	
Yes	42%
No	58%
Lymphovascular invasion	
Negative	79%
Positive	21%
Oestrogen receptor	
Negative	93%
Positive	7%
Progesterone receptor	
Negative	94%
Positive	6%
HER2	
Negative	99%
Positive	1%
Radiotherapy	69%
Chemotherapy	65%

Abbreviations: DCIS = ductal carcinoma *in situ*; MBC = metaplastic breast carcinoma.
^aCases were split at 2005 based on the number of cases, time of diagnosis and the length of follow-up period.

Table 2. Comparison between MBC diagnosed in the Western countries and Asian countries

	Western series	Asian series	P-value
Mean age in years (range)	61 (27–96)	57 (32–85)	0.017
Type of surgery			
Breast conserving surgery	95 (50)	21 (24)	<0.001
Mastectomy	96 (50)	67 (76)	
Tumour Size			
TNM pT1	46 (24)	16 (19)	0.797
TNM pT2	100 (52)	47 (55)	
TNM pT3&4	45 (24)	22 (26)	
Tumour subtypes			
Spindle cell	95 (34)	21 (24)	0.001
Squamous	47 (17)	30 (34)	
Mixed squamous and spindle	36 (13)	13 (15)	
Matrix producing	80 (29)	24 (27)	
Fibromatosis-like ^a	18 (7)	0 (0)	
Associated conventional carcinoma			
Yes	147 (58)	73 (88)	<0.001
No	105 (42)	10 (12)	
Invasive carcinoma grade			
1	4 (1)	2 (2)	0.009
2	71 (26)	7 (10)	
3	196 (73)	64 (88)	
LN stage			
1 (LN negative)	131 (73)	49 (68)	0.118
2 (1–3 positive nodes)	35 (19)	12 (16)	
3 (>3 positive nodes)	14 (8)	12 (16)	
Lymphovascular invasion			
Negative	150 (78)	68 (81)	0.596
Positive	42 (22)	16 (19)	
Radiotherapy	123 (68)	30 (50)	0.038
Chemotherapy	114 (61)	28 (81)	0.022

^aFibromatosis-like is a recently recognized subtype is a low grade spindle carcinoma diagnosed mainly in Nottingham a part of a consultation service. Follow-up was available for two cases only; therefore, they were grouped with spindle MBC.

When cases were stratified based on the centre of diagnosis, a significant difference in the outcome between centres was found ($X^2 = 21.35$, $P = 0.011$). There was a significant difference in the outcome between MBC diagnosed in Western countries and those diagnosed in Asian countries ($X^2 = 8.95$, $DF = 1$, $P = 0.003$). However, when locally advanced cases were excluded this difference was no longer significant ($X^2 = 2.71$, $DF = 1$, $P = 0.099$ and Table 3). Figure 1 shows the outcome of MBC from Western and Asian countries as compared with the control group. Therefore, further analysis of prognostic markers in MBC was performed with consideration to countries of origin (Western versus Asian) and stage of the disease (with and without stage pT3&4 tumours).

Prognostic markers in MBC. No association with outcome in terms of BCSS and DFI was found in MBC regarding patients' age, menopausal status, histological grade; even when analysed as low and high grade (grade 1/2 versus 3) or any of its components (pleomorphism, mitosis or tubule formation) when analysed separately. Similarly no association between outcome and the degree of tumour cellularity, presence of tumour necrosis or coexistence of conventional-type carcinoma or DCIS was found ($P > 0.05$).

There was a significant association between lymph node stage (Figure 2A) and presence of lymphovascular invasion and BCSS ($X^2 = 15.8$, $DF = 2$, $P < 0.0001$ and $X^2 = 7.6$, $DF = 2$, $P = 0.006$, respectively) but not with DFI. The same associations were observed in the Western and Asian subgroups with or without

Table 3. Cumulative survival of metaplastic carcinoma (including western and Asian subgroups) after exclusion of advanced-stage cases compared with early-stage conventional NST carcinoma

Interval start time in months	Number of patients entering interval	Number exposed to risk	Cumulative proportion surviving at end of interval
MBC			
30	285	242	0.85
60	162	137	0.77
90	98	78	0.74
120	54	46	0.72
150	35	27	0.67
Western			
30	145	122	0.88
60	84	70	0.78
90	48	36	0.76
120	23	20	0.72
150	15	11	0.59
Asian			
30	63	53	0.96
60	40	36	0.85
90	27	22	0.85
120	16	14	0.85
150	10	8	0.85
IDC NST			
30	284	282	0.91
60	254	254	0.80
90	222	210	0.76
120	188	169	0.74
150	144	116	0.71

Abbreviations: IDC NST = invasive ductal carcinoma of no special type; MBC = metaplastic breast carcinoma.

inclusion of locally advanced (pT3&4) cases. TNM pT stage was correlated with outcome ($X^2 = 10.3, P = 0.006$ and $X^2 = 11.5, P = 0.003$ for BCSS and DFI, respectively); however, when pT3&4 cases were excluded, these associations were no longer significant.

There was an association between MBC histologic subtypes and BCSS and DFI ($X^2 = 13.9, P = 0.008$ and $X^2 = 6.7, P = 0.01$, respectively). The difference in the outcome between matrix producing and squamous carcinomas was significant and both were associated with a better prognosis while spindle and mixed spindle and squamous were associated with the worst prognosis and their outcome was not statistically different (Figure 3). These associations were maintained after exclusion of locally advanced cases ($X^2 = 7.4, P = 0.006$ and $X^2 = 6.2, P = 0.01$ for BCSS and DFI, respectively). Chemotherapy was associated with longer survival ($X^2 = 4.1, P = 0.045$) but, when locally advanced cases were excluded, this association lost its significance. No associations between radiotherapy and outcome were found. Table 4 shows multivariate cox regression analysis of MBC with and without locally advanced cases. This indicates that MBC subtype is an independent prognostic variable associated with BCSS and DFI.

DISCUSSION

Metaplastic carcinoma of the breast (MCB) remains as a poorly characterised subtype of breast cancer. Although MBC is rare, its recognition as a discrete entity is increasing (Pezzi *et al*, 2007; Tseng and Martinez, 2011; Lee *et al*, 2012). Most of the prognostic studies of MBC have been small and with conflicting results or included non-validated cases from population based databases

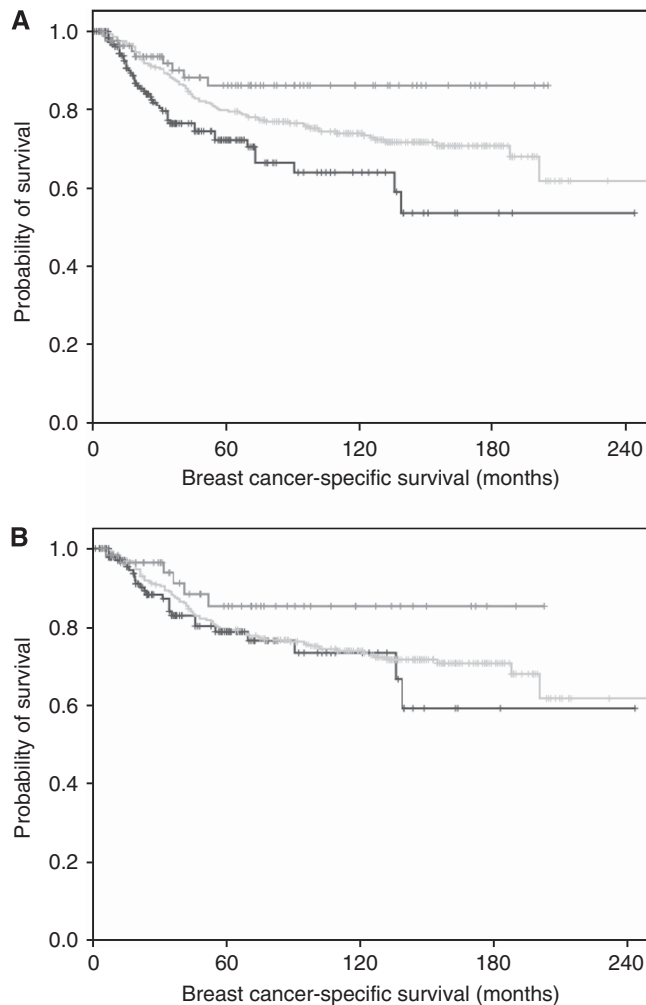


Figure 1. Correlation between MBC diagnosed in Western and Asian countries and outcome. (A) Comparison of breast cancer-specific survival (BCSS) of patients with metaplastic breast carcinoma diagnosed Asian countries (upper green curve; 88 patients) and Western countries (lower blue curve; 197 patients) as compared with the control group of conventional ductal carcinoma (middle grey curve; 285 patients) ($X^2 = 12.1, DF = 2, P = 0.002$). **(B)** Comparison of BCSS of same groups after exclusion of locally advanced cases (tumours > stage T2); Asian patients (upper green curve; 63 patients) and Western patients (lower blue curve; 145 patients) as compared with the control group of conventional ductal carcinoma (middle grey curve; 285 patients) ($X^2 = 2.9, DF = 2, P = 0.237$). A full color version of this figure is available at the *British Journal of Cancer* journal online.

(Foschini *et al*, 1993; Rayson *et al*, 1999; Hennessy *et al*, 2006; Tse *et al*, 2006; Luini *et al*, 2007; Pezzi *et al*, 2007; Jung *et al*, 2010; Yamaguchi *et al*, 2010; Bae *et al*, 2011; Tseng and Martinez 2011; Lee *et al*, 2012; Lester *et al*, 2012; Reis-Filho *et al*, 2012). In this large international multicentre series of histologically confirmed cases of MBC we have critically assessed the prognostic value of known prognostic variables and determine the outcome in comparison with matched conventional breast carcinoma of ductal/no specific type.

This study identified some factors that may explain the conflicting data published to date regarding clinicopathological and outcome data. MBC diagnosed in Asian countries showed longer survival compared with those diagnosed in Western countries. This can be partly explained by the over-representation of locally advanced cases in Western countries, other epidemiological factors or environmental determinants akin to those

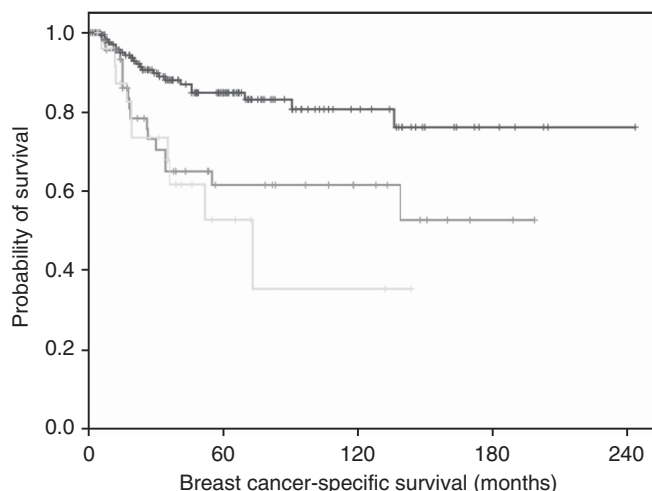


Figure 2. Association between lymph node stage in MBC and breast cancer-specific survival (node negative (180 patients) = upper blue, node positive 1–3 (46 patients) = middle green and node positive >3 (26 patients) = lower grey) ($\chi^2 = 15.8$, DF = 2, $P < 0.0001$). The same association was observed in Western and Asian subgroups with or without inclusion of locally advanced cases. A full color version of this figure is available at the *British Journal of Cancer* journal online.

observed in the stomach and upper gastrointestinal cancer (Gill *et al*, 2003). Other factors may include differences in treatment protocols. In this study, mastectomy rates and systemic chemotherapy use were higher in the Asian series.

The over-representation of metastatic advanced and locally advanced cases in some series may be one of the reasons for the reported poor outcome of MBS as the outcome in our series improved when these cases were excluded. Outcome analysis revealed that MBC is associated with shorter survival compared with matched conventional carcinoma. However, when analysis was restricted to early-stage cases (pT1&2) the outcome was not different to stage matched conventional carcinoma. Consistent with our findings, some authors have reported that, although MBC is associated with poor prognostic indicators, its outcome is comparable to matched conventional breast carcinomas (Beatty *et al*, 2006). When known prognostic variables in conventional breast carcinoma were analysed in the context of MBC, we found that lymph node stage and lymphovascular invasion were significant predictors of outcome. However, no association between histological grade or its components (mitosis, tubule formation and pleomorphism) (Rakha *et al*, 2008) or the Trojani grading system of sarcoma (mitosis, necrosis and differentiation) (Trojani *et al*, 1984) and outcome was detected. A finding that may represent the nature of the tumour with transdifferentiation of the malignant epithelial mammary tissue to a different histologic type. Tumour size also was not a significant prognostic factor.

One key observation in the current study is that the different subtypes of MBC are associated with distinct outcome. In this series, matrix producing carcinoma was associated with the best outcome while spindle and mixed spindle and squamous carcinomas were associated with the worst outcome and this was an independent prognostic variable (Beatty *et al*, 2006; Nayak *et al*, 2013). The better outcome of matrix producing carcinoma compared with other subtypes of MBC may be a reflection of its smaller primary tumour size and less frequent nodal metastasis and lymphovascular invasion (data not shown). In this study, it should be noted that few cases of fibromatosis-like metaplastic carcinoma with linked outcome data were included and no low-grade adenosquamous subtypes, which we consider as a distinct entity, were included in this study. Both of these subtypes

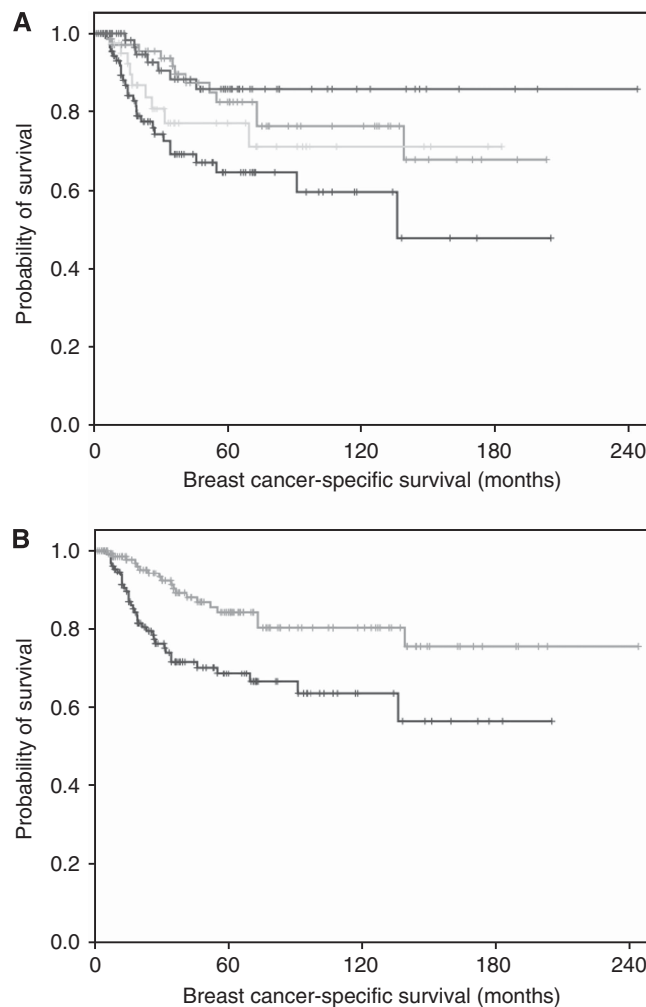


Figure 3. Association between MBC histologic subtype and outcome. (A) Association between breast cancer-specific survival and MBC histologic subtypes (matrix producing carcinoma (77 cases; upper purple), squamous (74 patients; upper middle green), mixed squamous and spindle (41 patients; lower middle grey) and spindle carcinoma (91 patients; lower blue) ($\chi^2 = 13.9$, DF = 3, $P = 0.008$). (B) Association between breast cancer-specific survival and MBC histologic subtype analysed as two groups (upper green; matrix producing and squamous combined (151 cases) and lower blue; spindle and mixed spindle and squamous (132 patients); $\chi^2 = 10.8$, DF = 1, $P = 0.001$). A full color version of this figure is available at the *British Journal of Cancer* journal online.

are recognized to have an excellent outcome (Van Hoesen *et al*, 1993; Gobbi *et al*, 1999).

Chemotherapy was associated with better outcome, although the effect was limited in early stage cases. Some authors have reported that systemic therapy may be less effective in MBC (Rayson *et al*, 1999; Gibson *et al*, 2005). In this study no association between radiotherapy and outcome was identified. Although Tseng and Martinez (2011) reported that radiotherapy is associated with improved overall survival I MBC, they included historical cases diagnosed from 1988 in their analysis and only 39% received RT with apparent low 10-year survival (53%). The effect of chemotherapy and radiotherapy on the outcome is best assessed in a focused randomized clinical trial.

This study has limitations. It is a retrospective study with the possibility of selection bias. Although the histological diagnosis of MBC was reviewed by breast pathologists, this was carried out locally in each institution with no central pathology review.

Table 4. Multivariate analysis of variables associated with outcome in metaplastic breast carcinoma with and without inclusion of locally advanced cases

	All MBC cases				MBC after excluding pT3&4			
	Hazard ratio	95%CI		P-value	Hazard ratio	95%CI		P-value
		Lower	Upper			Lower	Upper	
Breast cancer-specific survival								
TNM pT stage	2.067	1.175	3.637	0.012	1.529	0.519	4.501	0.441
LN stage	1.463	0.808	2.649	0.209	2.156	1.044	4.455	0.038
LVI	1.666	0.649	4.278	0.289	.984	0.258	3.746	0.981
Chemotherapy	0.305	0.143	0.650	0.002	.359	0.140	0.920	0.033
MBC subtype	1.061	0.927	1.213	0.391	1.201	1.030	1.399	0.019
Disease-free interval								
TNM pT stage	1.409	0.865	2.294	0.169	1.662	0.645	4.287	0.293
LN stage	1.284	0.739	2.229	0.375	1.486	0.750	2.944	0.256
LVI	1.393	0.545	3.558	0.488	0.593	0.144	2.438	0.468
Chemotherapy	0.570	0.288	1.127	0.106	0.605	0.273	1.341	0.216
MBC subtype	1.173	1.041	1.322	0.009	1.313	1.146	1.504	0.0001

Abbreviations: LN=lymph node; LVI=lymphovascular invasion; MBC=metaplastic breast carcinoma; TNM=tumour node metastasis.

In conclusion, this study provides evidence-based data that MBC is a heterogeneous disease encompassing biologically different tumour classes with variable outcome. Although the behaviour of MBC overall is not different to matched conventional forms of ductal/NST invasive breast carcinoma, the pattern of relevant prognostic variables in MBC is different from the spectrum of well-established variables in conventional breast carcinoma. Tumour histological subtype of MBC provides independent prognostic information. Both observations should be considered when managing MBC patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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