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Prognosis of medullary breast cancer: analysis of 13 International Breast Cancer Study Group (IBCSG) trials

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Background: To evaluate whether medullary breast cancer has a better prognosis compared with invasive ductal tumors.

Methods: Among 12 409 patients, 127 were recorded as invasive medullary tumors and 8096 invasive ductal tumors. Medullary and ductal invasive tumors were compared with regard to stage, age at diagnosis, grade, hormone receptor status, peritumoral vascular invasion, and local and systemic treatment. Pattern of relapse, distant recurrence-free interval (DRFI), and overall survival (OS) were determined for both histological groups. Two cohorts were investigated: a full cohort including the pathologist-determined medullary histology without regard to any other tumor features and a cohort restricted to patients with ER-negative grade 3 tumors.

Results: Fourteen-year DRFI and OS percents for medullary tumors ($n = 127$) and invasive ductal tumors ($n = 8096$) of the full cohort were 76% and 64% [hazard ratio (HR) 0.52, $P = 0.0005$] and 66% and 57% (HR = 0.75, $P = 0.03$), respectively. For the restricted cohort, 14-year DRFI and OS percents for the medullary ($n = 47$) and invasive ductal tumors ($n = 1407$) were 89% and 63% (HR 0.24, $P = 0.002$) and 74% and 54% (HR = 0.55, $P = 0.01$), respectively. Competing risk analysis for DRFI favored medullary tumors (HR medullary/ductal = 0.32; 95% confidence interval = 0.13–0.78, $P = 0.01$).

Conclusion: Medullary tumors have a favorable prognosis compared with invasive ductal tumors.

Key words: breast cancer, histology, invasive ductal, medullary, prognosis

introduction

Medullary carcinomas are rare breast tumors that account for <5% of invasive breast carcinomas [1–3]. The diagnosis of medullary carcinoma is usually defined by histologic diagnostic criteria proposed by Ridolfi et al. [4]. These histopathologic features include: lymphoplasmacytic infiltration, noninvasive microscopic circumscription, syncytial growth pattern >75%, and grade 2 or 3 nuclei. Despite these well-defined morphological features, medullary tumor diagnoses have poor reproducibility. Although several simplified classifications of a medullary phenotype have been proposed in order to increase reproducibility, the Ridolfi criteria remain the most generally accepted [5, 6]. Results of gene expression profiling show that medullary carcinoma may be a subtype of basal breast cancers, and a more modern definition would consider immunohistochemical results indicating negative estrogen, progesterone, and HER2 receptors. However, positive estrogen receptors (ER) and progesterone receptors (PgR) have been reported in up to 30%–40% of cases, and HER2 overexpression in ~10% of tumors diagnosed as medullary subtype [7–14], leaving the diagnosis of medullary breast cancer an area of controversy.

Data on the prognosis of medullary breast cancer are also conflicting. Some studies have indicated that this histologic type is associated with a favorable prognosis despite its association with biological features, which usually characterize a more aggressive subtype [2, 4, 15–18]. Other studies do not confirm this observation and some report survival rates similar to the invasive ductal type 'not otherwise specified' (NOS) [19–22].

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In order to clarify the prognosis of patients diagnosed with medullary breast carcinoma, we compared the clinicopathological features and outcomes of patients diagnosed with medullary carcinoma with those having invasive ductal tumors NOS. Data were obtained from 13 International Breast Cancer Study Group (IBCSG) trials conducted from 1978 through 1999. Recognizing the changing criteria over time, we defined two cohorts. The 'full cohort' includes the pathologist-determined histology without regard to any other tumor features, and the 'restricted cohort' is a more pure classification restricted to patients with ER-negative grade 3 tumors. In studies describing both ER and grade in medullary subtypes, all, or at least the vast majority, of the tumors were characterized as ER negative and of poor grade [9, 13, 23, 24]. Thus, we considered the classification using these additional features as more appropriate. We further limited the description of our restricted cohort according to ER status, since almost all ER-negative tumors are without PgR expression and PgR expression has only been described in a subset of reports [25]. In order to have the proper comparator group, we matched the full cohort to all invasive ductal tumors and the restricted cohort to the ER-negative, poor grade invasive ductal tumors. In each cohort, we identified patients as having tumor histology of medullary breast carcinoma or invasive ductal carcinoma NOS.

patients and methods

patients

Among the 12 409 patients enrolled in 13 IBCSG trials (conducted from 1978 to 1999) [26–38], 127 were recorded as having medullary invasive tumors, 8096 invasive ductal tumors NOS, and 4186 other tumor types (including atypical medullary) (supplemental Table S1, available at *Annals of Oncology* online; Table 1). All 13 trials included patients with early breast cancer and studied the timing and duration of chemoendocrine treatments. Histology was determined by central pathology review of submitted hematoxylin- and eosin-stained slides in 11 of the 13 trials (trials I–V, VIII, IX, 11–14) and by local review for the remaining two (trials VI and VII, $n = 2687$) where central review was not available. The 'full cohort' includes all patients recorded as either having medullary or ductal NOS invasive tumors. The 'restricted cohort' is a subset of the full cohort restricted to those with grade 3 and ER-negative tumors: 47 patients with medullary invasive tumors and 1407 with invasive ductal NOS tumors (supplemental Figure S1, available at *Annals of Oncology* online).

Patients with medullary and invasive ductal tumors were compared within the two defined cohorts with regard to age at diagnosis, menopausal status, local and systemic treatment, nodal status, tumor size, peritumoral vessel invasion (PVI), grade, and hormone receptor status.

The trials were conducted according to good clinical practice and in accordance with human investigation laws in the participating countries at the time of patient enrollment.

statistical methods

For the 13 trials, the protocol-defined primary end point was disease-free survival (DFS), defined as the time from randomization to the first occurrence of a breast event (local, regional, distant recurrence; contralateral breast event), a second (non-breast) malignancy, or a death before a cancer event. For this report with long-term follow-up, the more relevant end points used were distant recurrence-free interval (DRFI) and overall survival (OS). DRFI was defined as the time from randomization to first distant recurrence. Local and regional recurrences, contralateral breast and second non-breast events were ignored and follow-up continued until the first distant recurrence. Deaths without distant recurrences were censored. OS was defined as the time from randomization to death. DFRI and OS were presented using Kaplan–Meier curves. Log-rank P values of DFRI and OS were stratified by pathologist. There were four strata: one for each of the three central laboratories (the central laboratory changed three times over the 20-year period covered by these trials) and one strata for trials VI and VII (trials without central pathologic review). Competing risk regression models [39] were used to account for the competing risk of distant breast cancer events with other DFS events (i.e. local and regional

Table 1. Incidence of medullary and invasive ductal carcinomas among the 13 International Breast Cancer Study Group trials analyzed

	All patients (full cohort)		Patients with grade 3 and estrogen receptor-negative tumors (restricted cohort)	
	Medullary	Ductal	Medullary	Ductal
Total patients (% total trial accrual)	127 (1)	8096 (65)	47 (0.4)	1407 (11)
Trials with central pathology review				
I	13	306	5	34
II	4	216	0	29
III	19	289	3	24
IV	8	206	3	10
V	18	1701	11	350
VIII	8	693	6	135
IX	5	1065	5	178
11	1	98	0	1
12	0	277	0	2
13	0	799	0	247
14	3	622	3	198
Trials with local pathology review				
VI	26	991	7	120
VII	22	833	4	79

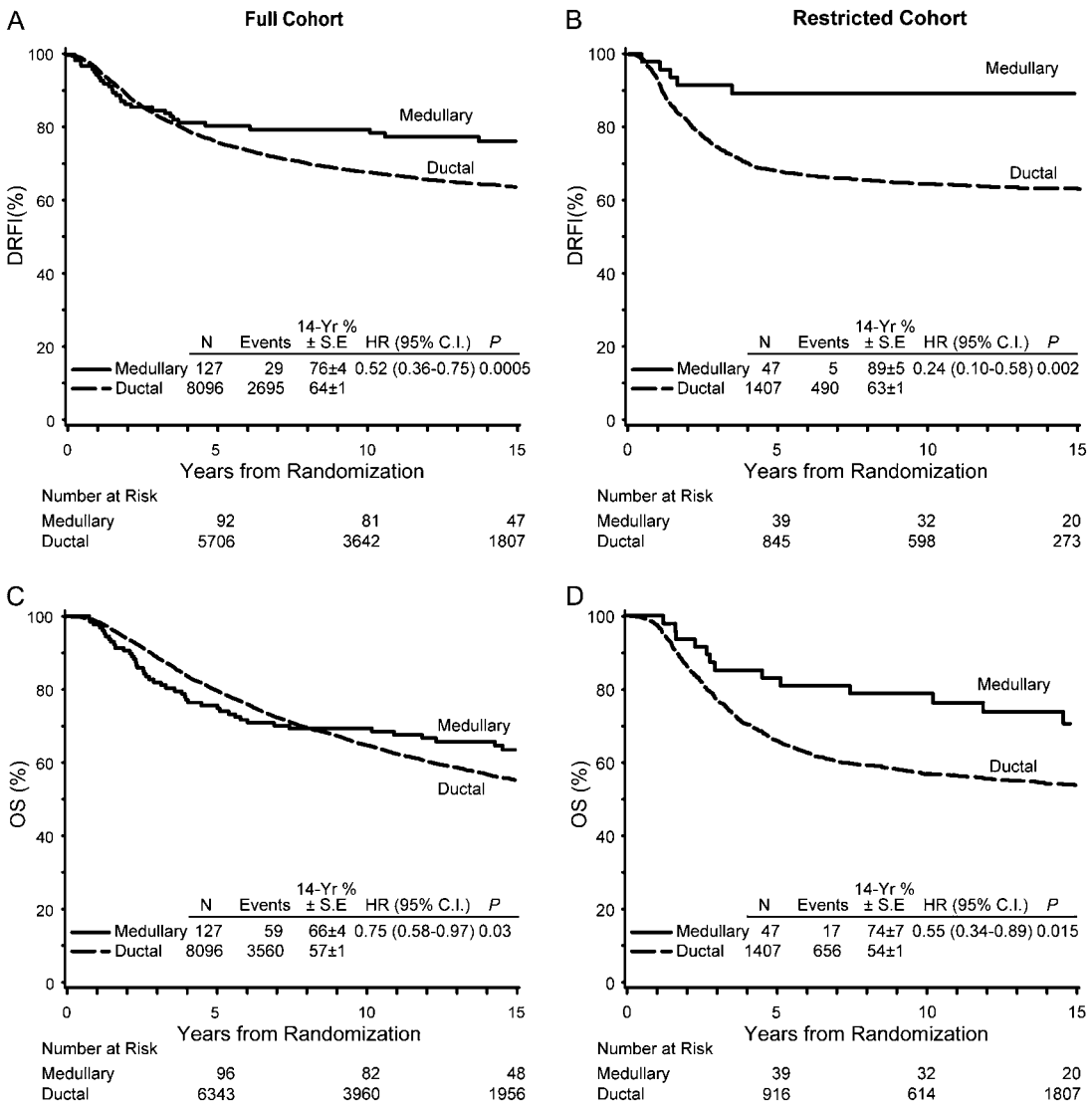

Figure 1. Kaplan–Meier plots of distant recurrence-free interval (DRFI) for patients with medullary and ductal tumors in the full cohort (A) and the cohort restricted to ER-negative grade 3 tumors (B); and overall survival (OS) in the full (C) and restricted (D) cohorts. CI, confidence interval; HR, hazard ratio; SE, standard error.

recurrences, contralateral breast cancers, second non-breast malignancies, and deaths without recurrence). The competing risk multivariate models included covariates for ER status, grade, nodal status, and tumor size. Patient and tumor characteristics were compared according to tumor type using the Fisher's exact test. No adjustment was made for multiple comparisons.

results

patient and tumor characteristics

The median follow-up for both the full and the restricted cohorts was 14 years. In both cohorts, medullary and ductal carcinomas differed in their presentation of tumor characteristics: nodal status, tumor size, grade, PVI, and hormone receptor status, with medullary tumors being associated with less favorable prognostic features with the single exception that medullary tumors were less likely to have PVI (Table 2). The majority of patients had some type of adjuvant systemic treatment: 67% of medullary cases and 77% of ductal cases in the full cohort received chemotherapy, and corresponding numbers in the restricted cohort were 68% versus 84% (Table 2). Of the 127 medullary cases in the full cohort, 64 were enrolled in trials with a chemotherapy randomization and 34 were assigned chemotherapy; corresponding numbers for the restricted cohort were 26 randomized and 14 assigned chemotherapy.

sites of first DFS event

Patients with ductal tumors had more local and distant sites of first DFS event, whereas those with medullary tumors had more second non-breast malignancies and deaths without prior cancer event (Table 3). These observations were similar in the two cohorts.

Table 2. Patient and tumor characteristics according to histologic type and cohort

	All patients (full cohort)			Patients with ER- and grade 3 tumors (restricted cohort)		
	Medullary	Ductal	*P* value*	Medullary	Ductal	*P* value*
Total patients	127	8096		47	1407	
Mean age at study entry	52.2	52.0		50.7	50.2	
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Menopausal status			0.86			0.66
Pre	62 (49)	4046 (50)		24 (51)	767 (55)	
Post	65 (51)	4050 (50)		23 (49)	640 (45)	
Surgery			0.06			0.74
Mastectomy	100 (79)	5748 (71)		35 (74)	1003 (71)	
BCS	27 (21)	2348 (29)		12 (26)	404 (29)	
Radiotherapy			0.07			1.00
Yes	25 (20)	2197 (27)		12 (26)	369 (26)	
No	102 (80)	5899 (73)		35 (74)	1038 (74)	
Nodal group			0.002			0.55
Node negative	26 (20)	2572 (32)		19 (40)	463 (33)	
1–3+ nodes	72 (57)	3382 (42)		17 (36)	555 (39)	
4+ nodes	29 (23)	2142 (26)		11 (23)	389 (28)	
Tumor size			0.002			
0–2 cm	44 (35)	3891 (49)		11 (23)	498 (36)	0.09
>2 cm	83 (65)	4085 (51)		36 (77)	895 (64)	
Missing	0	120		0	14	
Grade			<0.0001			
1	4 (4)	950 (13)				
2	9 (9)	3276 (45)				
3	83 (86)	3053 (42)		47 (100)	1407 (100)	
Missing	31	817				
PVI			<0.0001			<0.0001
Present	18 (19)	2963 (43)		6 (15)	586 (46)	
Absent	77 (81)	3995 (57)		34 (85)	695 (54)	
Missing	32	1138		7	126	
ER status			<0.0001			
Positive	18 (19)	4998 (68)				
Negative	77 (81)	2387 (32)		47 (100)	1407 (100)	
Missing	32	711				
PgR status			<0.0001			0.10
Positive	17 (19)	4124 (59)		3 (7)	220 (17)	
Negative	74 (81)	2899 (41)		43 (93)	1112 (83)	
Missing	36	1073		1	75	
Adjuvant systemic therapy			0.007**			0.008**
No adjuvant Rx	10 (8)	503 (6)		4 (9)	64 (5)	
ET alone	32 (25)	1317 (16)		11 (23)	162 (12)	
CT alone	60 (47)	3196 (39)		23 (49)	572 (41)	
CT + ET	25 (20)	3080 (38)		9 (19)	609 (43)	

Percentages sum within columns.

**P* values are calculated using Fisher's exact test. Missing categories are not included in the calculation of the *P* value.

***P* values compare chemotherapy versus no chemotherapy percents.

BCS, breast-conserving surgery; CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; PgR, progesterone receptor; PVI, peritumoral vascular invasion; Rx, treatment.

distant recurrence-free interval

The Kaplan–Meier curves in the full cohort show that the two histologic types had similar DRFI for the first 4 years, but thereafter, the curves split with consistently better outcome for the medullary subtype and a statistically significant overall DRFI [stratified log-rank test hazard ratio (HR) medullary/ductal = 0.52, 95% confidence interval (CI) = 0.36–0.75, *P* = 0.0005; Table 4, Figure 1A]. An even more pronounced difference was observed in the restricted cohort (DRFI HR medullary/ductal = 0.24, 95% CI = 0.10–0.58, *P* = 0.002; Table 4, Figure 1B) with the Kaplan–Meier curves diverging earlier. We note that because the hazards are not proportional,

Table 3. Sites of first disease-free survival (DFS) event according to histologic type and cohort

	All patients (full cohort)		Patients with estrogen receptor- and grade 3 tumors (restricted cohort)	
	Medullary	Ductal	Medullary	Ductal
Total patients	127	8096	47	1407
No DFS event	58 (46)	3577 (44)	26 (55)	642 (46)
Breast cancer-related	44 (35)	3770 (47)	14 (30)	674 (48)
DFS events				
Local	6 (5)	666 (8)	0	94 (7)
Contralateral breast	7 (6)	333 (4)	4 (9)	44 (3)
Regional	8 (6)	493 (6)	5 (11)	116 (6)
Distant (as first site)	23 (18)	2278 (28)	5 (11)	420 (30)
Distant soft tissue	4 (3)	129 (2)	0	33 (2)
Bone	6 (5)	880 (11)	1 (2)	105 (7)
Viscera	13 (10)	1269 (16)	4 (9)	282 (20)
Non-breast cancer-related events	25 (9)	749 (29)	7 (6)	91 (15)
Second primary non-breast	12 (9)	362 (4)	3 (6)	49 (3)
Death without prior cancer event	11 (9)	360 (4)	3 (6)	39 (3)
Unknown	2 (2)	27 (0.3)	1 (2)	3 (0.2)

the hazard rates are not constant over time. Therefore, the hazard rates reported represent an average over the entire follow-up period and the *P* values reflect the statistical significance of these HRs. In any case, the overall outcome for the medullary cohort is superior to that of the ductal cases. When the two subtypes were compared according to nodal status, similar results were observed in node-negative and node-positive subgroups, although the differences were statistically significant only among the patients with node-positive disease. DRFI was significantly better for medullary tumors in both cohorts both with and without adjuvant chemotherapy (Table 4). Among medullary cases in the full cohort, 10 of 34 randomly assigned chemotherapy had a distant recurrence compared with 7 of 34 not assigned chemotherapy; corresponding numbers for the restricted cohort were 2 of 14 compared with 1 of 12.

Comparisons between medullary and invasive ductal cohorts in terms of DFS were similar to those based on DRFI (data not shown).

overall survival

There also was a statistically significant difference in OS between the tumor histologic types for both the full cohort (OS HR medullary/ductal = 0.75, 95% CI = 0.58–0.97, $P = 0.03$; Table 4, Figure 1C) and for the restricted cohort (OS HR medullary/ductal = 0.55, 95% CI = 0.34–0.89, $P = 0.01$; Table 4, Figure 1D). When patients with medullary tumors were compared with those with ductal tumors in subgroups defined by nodal status, the OS for the medullary category was better in all cases, significantly so for the node-positive cohort (Table 4). When negative PgR status was added to the characterization of the restricted medullary cohort, the outcome did not change (data not shown).

competing risks

A secondary analysis was carried out focusing on the competing risk of distant breast cancer events with non-distant DFS events. While the competing risk curves for the full cohort were nonproportional (i.e. the curves cross) (Figure 2A), the curves restricted to patients with ER-negative grade 3 tumors were approximately proportional (Figure 2B). The result of the competing risk modeling in this restricted cohort indicated that medullary tumors had a significantly better prognosis than ductal carcinoma (HR medullary/ductal = 0.32, 95% CI = 0.13–0.78, $P = 0.01$). The result did not change after controlling for nodal status and tumor size (HR medullary/ductal = 0.32, 95% CI = 0.13–0.78, $P = 0.01$).

discussion

In our analysis of 12 409 patients, we identified only 127 (1.0%) medullary carcinomas, a frequency similar or slightly lower than in other published reports [1–3]. In both the full cohort and the restricted cohort, patients with medullary carcinomas had better outcomes overall compared with patients with invasive ductal carcinomas, despite medullary tumors being associated with biological features usually considered unfavorable. In fact, the 14-year DRFI of 89% in the restricted cohort of ER-negative grade 3 tumors was surprisingly good in this supposedly poor prognostic population. Our results thus confirm other reports that observed a superior outcome of tumors with medullary histology compared with invasive ductal tumors [2, 4, 15–18].

In subgroups defined by nodal status, a reduction in risk of distant recurrence for medullary cancers was observed for both node-negative and node-positive groups, although the differences were only statistically significant in the node-positive group. The lack of significance in the node-negative

Table 4. Distant relapse-free interval and overall survival according to histologic type

Distant recurrence-free interval					
	N	Distant recurrence	14-year DRFI % ± SE	HR (95% CI)	*P* value*
Full cohort				0.52 (0.36–0.75)	0.0005
Medullary	127	29	76 ± 4		
Ductal	8096	2695	64 ± 1		
Node-negative				0.53 (0.17–1.65)	0.27
Medullary	26	3	88 ± 6		
Ductal	2572	486	80 ± 1		
Node-positive				0.54 (0.37–0.80)	0.002
Medullary	101	26	73 ± 5		
Ductal	5524	2209	57 ± 1		
Chemotherapy				0.57 (0.37–0.87)	0.009
Medullary	85	22	72 ± 5		
Ductal	6276	2190	63 ± 1		
No chemotherapy				0.41 (0.19–0.87)	0.02
Medullary	42	7	85 ± 6		
Ductal	1820	505	70 ± 1		
Restricted cohort				0.24 (0.10–0.58)	0.002
Medullary	47	5	89 ± 5		
Ductal	1407	490	63 ± 1		
Node-negative				0.40 (0.10–1.62)	0.20
Medullary	19	2	89 ± 7		
Ductal	463	107	76 ± 2		
Node-positive				0.22 (0.07–0.69)	0.01
Medullary	28	3	89 ± 6		
Ductal	944	383	57 ± 2		
Chemotherapy				0.28 (0.10–0.76)	0.01
Medullary	32	4	88 ± 6		
Ductal	1181	415	63 ± 1		
No chemotherapy				0.14 (0.02–0.98)	0.05
Medullary	15	1	93 ± 6		
Ductal	226	75	65 ± 3		
Overall survival (OS)					
	N	**Deaths**	**14-year OS % ± SE**	**HR (95% CI)**	***P* value***
Full cohort				0.75 (0.58–0.97)	0.03
Medullary	127	59	66 ± 4		
Ductal	8096	3560	57 ± 1		
Node-negative				0.88 (0.44–1.76)	0.71
Medullary	26	8	80 ± 8		
Ductal	2572	738	73 ± 1		
Node-positive				0.76 (0.57–1.00)	0.05
Medullary	101	51	62 ± 5		
Ductal	5524	2822	49 ± 1		
Chemotherapy				0.71 (0.51–1.00)	0.05
Medullary	85	35	65 ± 5		
Ductal	6276	2742	57 ± 1		
No chemotherapy				0.67 (0.44–1.02)	0.06
Medullary	42	24	67 ± 7		
Ductal	1820	818	58 ± 1		
Restricted cohort				0.55 (0.34–0.89)	0.01
Medullary	47	17	74 ± 7		
Ductal	1407	656	54 ± 1		
Node-negative				0.86 (0.38–1.94)	0.71
Medullary	19	6	78 ± 10		
Ductal	463	149	70 ± 2		

Continued

Table 4. *Continued*

	Overall survival (OS)				
	N	Deaths	14-year OS % ± SE	HR (95% CI)	*P* value*
Node-positive				0.53 (0.29–0.98)	0.04
Medullary	28	11	71 ± 9		
Ductal	944	507	46 ± 2		
Chemotherapy				0.52 (0.29–0.95)	0.03
Medullary	32	11	74 ± 8		
Ductal	1181	554	53 ± 2		
No chemotherapy				0.52 (0.22–1.21)	0.13
Medullary	15	6	73 ± 11		
Ductal	226	102	58 ± 3		

Log-rank *P* values are stratified by pathologist review.

DRFI, distant recurrence-free interval; CI, confidence interval; HR, hazard ratio; OS, overall survival; SE, standard error.

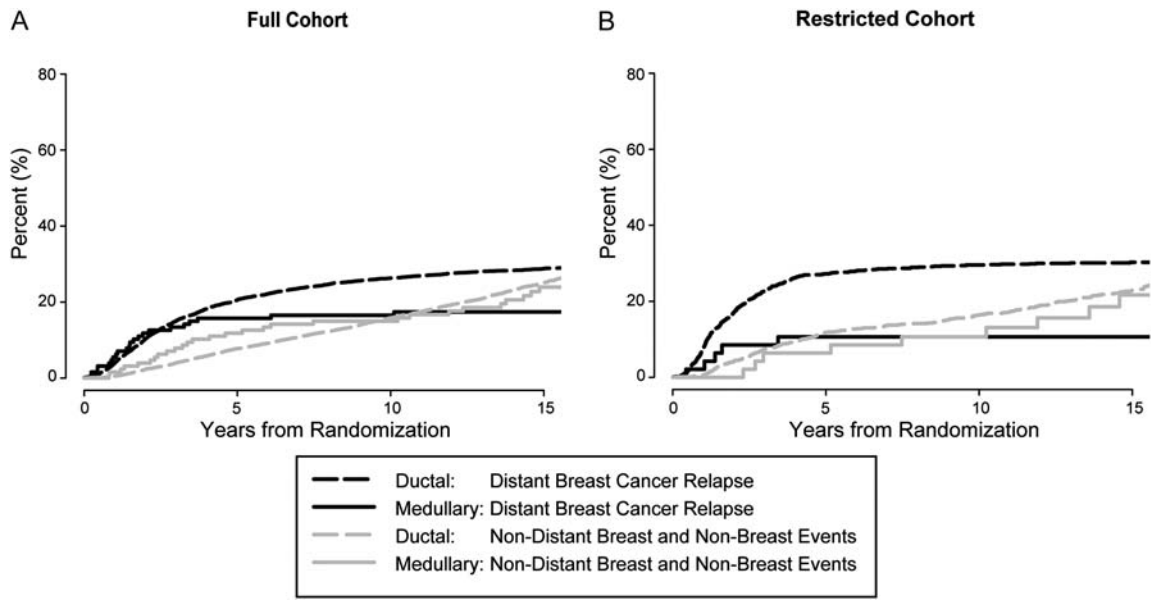

Figure 2. Cumulative incidence plots of competing risk of distant and non-distant events for full cohort for medullary versus ductal tumors: competing causes of failure with the full (A) and restricted cohorts (B).

group may be due to the smaller number of cases, as several other reports describe better outcomes for medullary tumors irrespective of the nodal status [4, 13].

The lower risks of distant recurrence and death for medullary tumors compared with invasive ductal carcinomas were seen irrespective of the application of adjuvant chemotherapy. However, our data do not permit reliable conclusions regarding the role of adjuvant chemotherapy for patients with medullary tumors. Although patients with medullary tumors appear to have a relatively good prognosis even without chemotherapy, those with invasive ductal disease also have a better outcome without chemotherapy, indicating a selection bias to enroll patients with better prognosis in trials with a no chemotherapy option. Chemotherapy was a randomized option for very few patients with medullary tumors. Furthermore, several different chemotherapy regimens were given with or without endocrine therapy without considering ER status in the earlier trials. Thus, because the role of chemotherapy for medullary carcinomas in the restricted cohort is less certain than for invasive ductal carcinomas, further studies are needed to clarify this issue.

In our study, we were able to report on the sites of first recurrences, a feature not commonly reported by others. The majority of first recurrences were distant and we found that both local relapse and distant relapse were less frequently observed in the medullary type than in the invasive ductal type in both cohorts.

Although the main conclusions were similar in the full and restricted cohorts (i.e. improved outcome and association with poorer disease characteristics), we found differences between the two cohorts. The reduction in the risk of a distant recurrence in medullary tumors compared with invasive ductal

was higher in the restricted cohort (76%) than in the full cohort (48%). In the full cohort, the incidence of distant recurrence separated after 4 years, with few events occurring thereafter in the medullary group, whereas events in the invasive ductal group continued to be observed beyond 4 years. In the restricted cohort, the separation of events occurred earlier and after 4 years, there were very few distant recurrences in either the medullary or invasive ductal (G3, ER −) groups. The distribution of events over time is typical for ER-negative tumors and thus not surprising [40]. Nevertheless, there was a substantial advantage in the control of distant recurrence in the medullary type during the first 5 years after diagnosis, which persisted over time.

These outcome distinctions between the two cohorts, with much clearer differences in the restricted group compared with its control group, support the suggestion that the definition of the medullary subtype seems to be most informative when restricted to ER-negative and poor grade tumors. In addition, the pattern of relapse occurring almost exclusively in the first 4 years in the restricted cohort further confirms this view.

These observations support recent reports linking the medullary tumors to myoepithelial features and the basal-like phenotype [14, 23, 41, 42], which in most cases is immunohistochemically characterized by negative expression of ER, PgR, and HER2 (triple-negative tumors). Interestingly, microarray-based analyses showed that medullary carcinomas and invasive ductal tumors with a basal-like phenotype have distinct molecular characteristics [9, 23] even though they share similar biological features. In medullary breast cancer, genes involved in T_h1 immune response including interleukins, interferon regulatory factors, and T_h1 cytokines and genes related to the apoptosis pathway were upregulated. By contrast, genes involved in the remodeling of the cytoskeleton and genes associated with cell invasiveness were downregulated in medullary carcinomas [43]. These different molecular characteristics may account for the favorable outcome of medullary carcinomas and suggest that the group of basal-like tumors constitutes a heterogeneous group of carcinomas.

In conclusion, our analysis, based on a compilation of data from 13 trials conducted by a single cooperative group, demonstrates an improved outcome for patients with medullary breast carcinomas compared with invasive ductal carcinomas despite the former's unfavorable biologic features. These differences in outcome were most pronounced within the restricted cohort confined to patients with ER-negative grade 3 tumors and we suggest that lack of ER expression and poor grade should be part of the definition of medullary breast cancer. The definition of medullary subtype used in our restricted cohort does not include information on the HER2 status. However, as most medullary cancers lack HER2 overexpression/amplification, our conclusions would most likely not change if HER2 was known. Currently, ER-negative and in particular triple-negative tumors (used as surrogate for basal-like phenotype even though not completely concordant) will be treated on average with more intensive chemotherapy due to their prognosis and the observation that these tumors are more sensitive to chemotherapy than others [44, 45]. However, the favorable prognosis of medullary tumors and the different molecular pattern of these tumors, compared with others linked to the basal-like phenotype, raise questions about this treatment approach. Clinical data are lacking on the efficacy of adjuvant chemotherapy in this patient population and whether less adjuvant treatment should be given is still an area of controversy. The NCCN guidelines recommend to treat early medullary cancers as other infiltrating ductal tumors [46], whereas the St Gallen Consensus recommendations suggest that medullary carcinomas may not require adjuvant cytotoxics if node-negative [47]. Based on the excellent 14-year DRFI in the medullary-restricted cohort, our data support this recommendation. Thus, we suggest that considering the histologic subtype may be helpful when deciding the appropriate adjuvant treatment assuming that the breast tumor is reliably classified as a medullary carcinoma. Lessons learned from rare tumors will improve our understanding of the biology of breast cancer and may help in further refinement and individualizing adjuvant treatment.

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disclosure

The authors have declared no conflicts of interest.

references

1. Dendale R, Vincent-Salomon A, Mouret-Fourme E et al. Medullary breast carcinoma: prognostic implications of p53 expression. Int J Biol Markers 2003; 18: 99–105.
2. Reinfuss M, Stelmach A, Mitus J et al. Typical medullary carcinoma of the breast: a clinical and pathological analysis of 52 cases. J Surg Oncol 1995; 60: 89–94.
3. Rakha EA, Putti TC, Abd El-Rehim DM et al. Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. J Pathol 2006; 208: 495–506.
4. Ridolfi RL, Rosen PP, Port A et al. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. Cancer 1977; 40: 1365–1385.

5. Pedersen I, Holck S, Mouridsen HT et al. Prognostic comparison of three classifications for medullary carcinoma of the breast. Histopathology 1999; 34: 175–186.
6. Eichhorn JH. Medullary carcinoma, provocative now as then. Semin Diagn Pathol 2004; 21: 65–73.
7. Rosen PP, Lesser ML, Arroyo CD et al. Immunohistochemical detection of HER2/neu in patients with lymph node negative breast cancer. Cancer 1995; 75: 1320–1326.
8. Foschini MP, Eusebi V. Rare (new) entities of the breast and medullary carcinoma. Pathology 2009; 41: 48–56.
9. Bertucci F, Finetti P, Cervera N et al. Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. Cancer Res 2006; 66: 4636–4644.
10. Pertschuk LP, Kim DS, Nayer K et al. Immunocytochemical estrogen and progestin receptor assays in breast cancer with monoclonal antibodies. Cancer 1990; 66: 1663–1670.
11. Jensen ML, Kier H, Melsen F. Medullary breast carcinoma vs. poorly differentiated ductal carcinoma: an immunohistochemical study with keratin 19 and oestrogen receptor staining. Histopathology 1996; 29: 241–245.
12. Orlando L, Renne G, Rocca A et al. Are all high grade breast cancers with no steroid receptor hormone expression alike? The special case of the medullary phenotype. Ann Oncol 2005; 16: 1094–1099.
13. Pedersen L, Zedeler K, Holck S et al. Medullary carcinoma of the breast. Prevalence and prognostic importance of classical risk factors in breast cancer. Eur J Cancer 1995; 31A: 2289–2295.
14. Flucke U, Flucke MT, Hoy L et al. Distinguishing medullary carcinoma of the breast from high-grade hormone receptor-negative invasive ductal carcinoma: an immunohistochemical approach. Histopathology 2010; 56: 852–859.
15. Pedersen L, Zedeler K, Holck S et al. Medullary carcinoma of the breast, proposal for a new simplified histopathological definition. Br J Cancer 1991; 63: 591–595.
16. Pedersen L, Holck S, Schiødt T et al. Medullary carcinoma of the breast, prognostic importance of characteristic histopathological features evaluated in a multivariate Cox analysis. Eur J Cancer 1994; 30A: 1792–1797.
17. Gamel JW, Meyer JS, Feuer E et al. The impact of stage and histology on the long-term clinical course of 163.808 patients with breast carcinoma. Cancer 1996; 77: 1459–1464.
18. Vu-Nishino H, Tavassoli FA, Ahrens WA et al. Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (BCT). Int J Radiat Oncol Biol Phys 2005; 62: 1040–1047.
19. Vo T, Xing Y, Meric-Bernstam F et al. Long-term outcomes in patients with mucinous, medullary, tubular, and invasive ductal carcinomas after lumpectomy. Am J Surg 2007; 194: 527–531.
20. Fisher ER, Kenny JP, Sass R et al. Medullary cancer of the breast revisited. Breast Cancer Res Treat 1990; 16: 215–229.
21. Cook DL, Weaver DL. Comparison of DNA content, s-phase fraction and survival between medullary and ductal carcinoma of the breast. Am J Clin Pathol 1995; 104: 17–22.
22. Fisher ER, Anderson S, Redmond C et al. Pathologic findings from the National Surgical Adjuvant Breast Project protocol B-06. Cancer 1993; 71: 2507–2514.
23. Vincent-Salomon A, Gruel N, Lucchesi C et al. Identification of typical medullary breast carcinoma as a genomic sub-group of basal-like carcinomas, a heterogeneous new molecular entity. Breast Cancer Res 2007; 9: R24.
24. Rakha EA, Aleskandarany M, El-Sayed ME et al. The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast. Eur J Cancer 2009; 45: 1780–1787.
25. Rakha EA, El-Sayed E, Green RA et al. Biologic and clinical characteristics of breast cancer with single hormone receptor-positive phenotype. J Clin Oncol 2007; 25: 4772–4778.
26. Ludwig Breast Cancer Study Group. A randomized trial of adjuvant combination chemotherapy with or without prednisone in premenopausal breast cancer patients with metastases in one to three axillary lymph nodes. Cancer Res 1985; 45: 4454–4459.
27. Ludwig Breast Cancer Study Group. Chemotherapy with or without oophorectomy in high-risk premenopausal patients with operable breast cancer. J Clin Oncol 1985; 3: 1059–1067.
28. Pagani O, Price KN, Gelber RD et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: A therapeutic target for a quarter of a century. Breast Cancer Res Treat 2009; 117: 319–324.
29. Colleoni M, Gelber S, Coates A et al. Influence of endocrine-related factors on response to perioperative chemotherapy for patients with node-negative breast cancer. J Clin Oncol 2001; 19: 4141–4149.
30. Ludwig Breast Cancer Study Group. Combination adjuvant chemotherapy for node-positive breast cancer. Inadequacy of a single perioperative cycle. N Engl J Med 1988; 319: 677–683.
31. The International Breast Cancer Study Group. Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. J Clin Oncol 1996; 14: 1885–1894.
32. The International Breast Cancer Study Group. Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. J Clin Oncol 1997; 15: 1385–1393.
33. Karlsson P, Sun Z, Braun D et al. Long term results of International Breast Cancer Study Group Trial VIII: adjuvant chemotherapy plus goserelin compared with either therapy alone for premenopausal patients with node-negative breast cancer. Ann Oncol 2011; 22: 2216–2226.
34. Aebi S, Sun Z, Braun D et al. Differential efficacy of three cycles of CMF followed by tamoxifen in patients with ER-positive and ER-negative tumors: long-term follow up on IBCSG Trial IX. Ann Oncol 2011; 22: 1981–1987.
35. Thürlimann B, Price KN, Gelber RD et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat 2009; 113: 137–144.
36. International Breast Cancer Study Group. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. Ann Oncol 2004; 15: 1749–1759.
37. International Breast Cancer Study Group. Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: IBCSG Trial 13-93. J Clin Oncol 2006; 24: 1332–1341.
38. International Breast Cancer Study Group. Effects of a treatment gap during adjuvant chemotherapy in node-positive breast cancer: results of International Breast Cancer Study Group (IBCSG) trials 13-93 and 14-93. Ann Oncol 2007; 18: 1177–1184.
39. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Amer Stat Assoc 1999; 94: 496–509.
40. Saphner T, Tomey T, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996; 14: 2738–2746.
41. Weigelt B, Horlings HM, Kreike B et al. Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 2008; 216: 141–150.
42. Jacquemier J, Padovani L, Rabayrol L et al. Typical medullary breast carcinomas have a basal/myoepithelial phenotype. J Pathol 2005; 207: 260–268.
43. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they?. Mol Oncol 2010; 4: 192–208.
44. Huober J, von Minckwitz G, Denkert C et al. Effect of neoadjuvant anthracycline-taxane based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010; 124: 133–140.
45. Liedtke C, Mazuoni C, Hess KR et al. Response to neoadjuvant chemotherapy and long-term survival in patients with triple negative breast cancer. J Clin Oncol 2008; 26: 1275–1281.
46. National Comprehensive Cancer Network (NCCN). NCCN Guidelines Version 2.2011. Breast Cancer. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (22 December 2011, date last accessed).
47. Goldhirsch A, Wood WC, Coates AS et al. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011; 22: 1736–1747.