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Original Article

Clinical implications of multifocality as a prognostic factor in breast carcinoma - a multivariate analysis study comprising 460 cases

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Abstract: Background: Multifocality is not listed among prognostic factors in international breast cancer guidelines. This study aims to analyze survival in multiple breast carcinomas (MFMC cc) compared to unifocal ones (UF cc), in order to assess the prognostic impact of multifocality. Methods: The study included 460 breast carcinomas (2002-2006) with a median follow-up time of 104 months (74-134 months). We assessed mortality rates, overall survival at 5 years and 10 years in general, overall survival at 5 and 10 years in MFMC cc compared to UF cc, as well as median survival and survival rate according to age, T status and axillary lymph node status in MFMC cc compared to UF cc. We carried out a multivariate analysis in order to identify independent predictor factors for survival. Results: 69/460 (15%) of cases were MFMC cc. Mortality rates were 56.5% in MFMC cc versus 45.1% (UF cc) (P = 0.08). 5-year overall survival was 55.9% in MFMC cc vs. 64.7% UF cc, and the 10-year overall survival was 34.9% MFMC cc vs. 52.7% UF cc (P = 0.27). Median survival in MFMC cc was 78 months (6.5 years), whereas in UF cc it was 126 months (10.5 years). However, in the multivariate analysis, survival was independently influenced only by tumor size and the presence of axillary lymph node metastases (P < 0.0001). Conclusion: Breast cancer multifocality is associated with higher general mortality rates, lower 5 and 10-year overall survival, yields a lower median survival, but it does not constitute an independent prognostic factor in multivariate analysis.

Keywords: Multiple breast carcinoma, survival, prognostic factor

Introduction

Breast carcinoma is the most frequent form of cancer in women, with an estimated prevalence of 3,763,070 cases in Europe in 2010 [1]. At the same time, breast carcinoma is the main cause of cancer mortality in women in the European Union [2]. Most of the breast carcinomas are unifocal (UF cc) however a variable proportion are multiple (multifocal/multicentric) (MFMC cc) and data regarding the prognosis of these tumors are contradictory. Multifocality is not listed among the traditional prognostic factors (tumor size, histological grade, axillary lymph node status) or among the second generation ones (ER, PR, Ki67 index and HER2 status) in breast carcinoma [3]. The aim of this study was to analyze survival in MFMC cc compared to UF ones, in order to assess the clinical impact of multifocality on prognosis, as data available in the literature does not show a consensus on this subject [4-7]. A second objective was to identify focality as an independent prognostic factor in breast carcinoma.

Material and methods

Patient selection

We carried out a retrospective study that included 460 cases that underwent surgical treatment for breast carcinomas at the Surgical

Table 1. Survival analysis in relation to multifocality in patients who underwent surgery and oncologic treatment for breast carcinoma (2002-2006)

Parameters	Categories (number)	Deaths n (%)	5-year survival (%)	10-year survival (%)	P
Focality	MFMC cc (69)	39 (56.5)	55.9	34.9	0.27
	UF cc (391)	176 (45.1)	64.7	52.7	HR: 0.68 IC: 0.46-1.02

Clinic Tirgu-Mures between January 2002 and December 2006 and which were consequently taken into evidence at the Oncology Department Tirgu-Mures and the Oncologic Institute Cluj-Napoca for the oncologic treatment. These 460 patients had undergone either total mastectomy or lumpectomy, with or without complete axillary lymph node dissection. Patient assignation to the UF cc or the MFMC cc categories, respectively, was accomplished using clinical, imaging (ultrasound and mammography) and pathologic gross and microscopic examinations. In this study, we defined multiple carcinomas as tumors having at least two histologically confirmed distinct invasive foci located within the same breast, detected at the same time and separated by "uninvolved" breast tissue, regardless of the distance between foci or localization (in the same quadrant/in different quadrants) [5]. Also, we defined as unifocal carcinomas the cases in which only one invasive tumor focus was detected throughout examination. Median follow-up time was 104 months (74-134 months). We assessed mortality rates, overall survival at 5 years and at 10 years in general, overall survival at 5 and 10 years in MFMC cc compared to UF cc, as well as the median survival and survival rate according to the age, T status and axillary lymph node status in MFMC cc compared to UF cc. The Ethics Committee of the University of Medicine and Pharmacy Tirgu-Mures approved this study, and all the procedures were performed in compliance with relevant laws and institutional guidelines.

Statistical analysis

Survival analysis was carried out using the Kaplan-Meier method, and differences were compared using the log-rank statistical significance test. Median follow-up time was calculated as the median observation interval for all patients as the time from surgery to the last follow-up. Overall survival was defined as the time from diagnosis to the date of patient's death or last known contact. Five-year/10-year survival rate measures survival at 5/10 years after diagnosis. Median survival is defined as the amount of time at which 50% of the patients have died and 50% have survived. Univariate and multivariate analysis in order to determine independent predictive factors for survival were carried out using a Cox regression model. Multivariate analysis of survival in breast carcinoma was carried out with independent variables: age, focality, T status and presence of metastases. Results were expressed as hazard ratios (Expβ) with 95% CIs. A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using the MedCalc statistical software.

Results

Of the 460 patients with breast carcinoma taken into evidence at the Oncology Department from Tirgu-Mures and Cluj-Napoca, 69 (15%) cases were MFMC cc, and 391 (85%) cases were UF cc.

The mortality rate in MFMC cc were 56.5% (39/69 cases) compared to 45.1% in UF cc (176/391 cases) (P = 0.08) (OR = 1.58). Overall 5-year survival rate was 63.3% and 10-year survival rate was 50.4% (P = 0.17).

Survival analysis in relation to focality in patients who underwent surgical and oncologic treatment for breast carcinoma is summarized in **Table 1**. 5-year survival was 55.9% in MFMC cc, compared to 64.7% in UF cc and 10-year survival was 34.9% in MFMC cc, versus 52.7% in UF cc ones (P = 0.27) (Hazard ratio = 0.68, IC = 0.46-1.02).

Survival rates at 5 and 10 years in patients under and over 50 years, according to tumor size status (T), with and without metastases, are shown in **Table 2**.

5-year survival in relation to age was 70.6% (MFMC cc) vs. 72.4% (in UF cc) (P = 0.88) (in patients under 50 years) and 49.8% (in MFMC cc) vs. 62.9% (in UF cc) (P = 0.1) (in patients

Table 2. Survival at 5 and at 10 years in patients with unifocal versus multiple breast carcinoma between 2002 and 2006 in relation to age, T status and axillary lymph node metastases

UF cc		Survival at 5 years		p	Survival at 10 years		p
		UF cc	MFMC cc		UF cc	MFMC cc	
Age	< 50	72.4%	70.6%	0.88	61.9%	38.8%	0.13
	> 50 years	62.9%	49.8%	0.10	49.1%	34.9%	0.08
T status	T1	84.2%	81.1%	0.97	78.2%	55.3%	0.05
	T2	59.2%	51.5%	0.52	41.4%	20.8%	0.04
	T3	41.1%	26.7%	0.47	29.5%	14.8%	0.04
N status	N + (with metastasis)	54.5%	53.2%	0.98	37%	28.6%	0.36
	N0 (without metastasis)	83.3%	83.3%	0.68	75.1%	55.6%	0.26

Table 3. Multivariate analysis of survival in breast carcinoma with independent variables: age and focality

Covariate	b	SE	P	Exp (b)	95% CI of Exp (b)
UF cc/MFMC cc	0.4046	0.1775	0.027	1.4987	1.0601 to 2.1188
Age group	0.3764	0.1853	0.046	1.4571	1.0153 to 2.0911

over 50 years). 10-year survival was 38.8% (in MFMC cc) vs 61.9% (in UF cc) (in patients under 50 years) (P = 0.13) and 34.9% (in MFMC cc) vs 49.1% (in UF c) (in patients over 50 years) (P = 0.08).

5-year survival analysis according to tumor size in UF cc versus MFMC cc did not reveal statistically significant differences between the two groups (**Table 2**) (pT1 cases 81.1% MFMC cc vs. 84.2% UF cc, P = 0.97; pT2 cases 51.5% MFMC cc vs. 59.2% UF cc, P = 0.52; and pT3 cases 26.7% MFMC cc vs. 41.1% UF cc, P = 0.47). However, data concerning 10-year survival rates in relation with tumor size show statistically significant differences between unifocal and multiple carcinomas: in pT1 cases survival rates were 55.3% (MFMC cc) vs. 78.2% (UF cc) (P = 0.05), in pT2 cases they were 20.8% (MFMC cc) vs. 41.4% (UF cc) (P = 0.04) and in pT3 cases they were 14.8% (MFMC cc) vs. 29.5% (UF cc) (P = 0.04).

We also encountered differences among groups in relation with axillary metastases, e.g. survival at 5 years in axillary positive cases was 53.2% in MFMC cc and 54.5% in UF cc (P = 0.98) and 10-year survival was 28.6% in MFMC cc cases versus 37% in UF cc with positive axilla (P = 0.36) (see **Table 2**).

The median survival in MFMC cc was 78 months or 6.5 years, and in UF cc it was 126 months or 10.5 years.

We carried out a Cox regression analysis in which the dependent variable was status (0-alive, 1-deceased), and the independent variables were focality and age at diagnosis. Survival is independently influenced both by age (over 50 de years, unfavorable) (P = 0.027) and by focality (multiple tumors, unfavorable prognosis) (P = 0.046) (**Table 3**).

By Cox regression analysis in which the dependent variable was status (0-alive, 1-deceased), and the independent variables were focality, age at diagnosis, T status and the presence of metastases, we found that survival is independently influenced only by T status (advanced T status, unfavorable) (P < 0.0001) and by the presence of axillary lymph node metastases (unfavorable prognosis) (P < 0.0001) (**Table 4**) while focality did not influence survival.

Discussion

Multifocality in breast cancer is a frequent phenomenon, whose prevalence may vary between 6-77% [8, 9]. In order to classify breast cancer, tumor-node-metastasis (TNM) staging has been considered the gold standard. The T category in multiple tumors is assessed by the largest tumor focus, multiplicity being accepted and included only by using the suffix (m) [10]. If more than one invasive focus is detected, the secondary invasive tumor foci will not be included in the tumor size estimation and the overall tumor burden does not have influence on which protocol is being selected for treatment [11], although many previous studies have demonstrated that multiple breast carcinoma is asso-

Table 4. Multivariate analysis of survival in breast carcinoma with independent variables: age, focality, T status andpresence of metastases

Covariate	b	SE	P	Exp (b)	95% CI of Exp (b)
UF cc/MFMC cc	0.1779	0.1981	0.36	1.1947	0.8118 to 1.7580
Age group	0.2894	0.2029	0.15	1.3356	0.8991 to 1.9839
T status	0.5412	0.1227	< 0.0001	1.7181	1.3525 to 2.1824
Axillary metastases	0.9492	0.1909	< 0.0001	2.5837	1.7807 to 3.7488

Table 5. Summary of studies comprising mortality rates in MFMC vs. UF carcinomas of the breast

Authors	Mortality rates		*p*-value
	MFMC cc	UF cc	
Dabakuyo et al [16]	50.83%	45.57%	0.0002
Boyages et al [17]	28.7%	18.7%	0.002
Egan et al [15]	15%/year	2.5%/year	NA

ciated with a higher risk for axillary lymph node metastases [12, 13], it may be associated with a higher risk of local relapse [8] and a poorer prognosis [14, 15]. Accurate estimation of prognosis is important for clinical decisions, such as whether to use more aggressive adjuvant therapies. By not including all foci of multiple breast carcinomas, estimates of the risk of recurrence and death may be understated, which could affect recommendations for adjuvant treatment [7].

In this study we found a higher mortality rate in MFMC cc compared to UF cc (56.5% vs. 45.1%) (P = 0.08), similar with other studies (as shown in **Table 5**).

Overall survival at 5-years in our study was 63.3%, and at 10-years was 50.4%, lower than data in the literature (82% at 5 years according to Dabakuyo, and 72% (Dabakuyo) or 70% (Allemani) at 10 years) [16, 18]. These results can be explained by the particular clinical and pathological data of the patients included in this study, by the fact that the majority of the patients (70.65%, 325/460) were diagnosed in an advanced stage (II-IV), with only 29.34% diagnosed in an early stage, and due to the lack of a national screening program in our country.

Survival analysis according to focality revealed that 5-year survival was 55.9% in MFMC cc, compared to 64.7% in UF cc and 10-year survival was 34.9% in MFMC cc, versus 52.7% in UF cc ones (P = 0.27) (Hazard ratio = 0.68, 95% CI = 0.46-1.02). These values were slightly lower in MFMC cc but without statistical significance, similar to other studies [9, 19, 20]. Other authors found statistically significant differences between survival rates according to lesion focality (e.g. Dabakuyo, Boyages) [16, 17] (**Table 6**). A systematic review and meta-analysis comprising 22 studies and 67.557 women concluded that women with MFMC cc had worse overall survival at 5-years compared to those with UF cc (OR 1.39; 95% CI 1.05-1.84, P = 0.02) [21].

Median survival in MFMC cc was 78 months or 6.5 years, and in UF cc it was 126 months or 10.5 years. Relative risk (hazard ratio) (HR) was 0.68, similar with a study carried out by Weissenbacher et al. [4], which revealed that median survival was 203.3 months in MFMC cc compared to 221.6 months in UF cc (P < 0.001, log-rank test) [4]. Ustaalioglu et al [20]. reported a significantly lower median survival rate in patients with MFMC cc than those with UF cc (55 vs. 137 months, P < 0.001) [20].

In our study, the analysis of the overall survival in relation with the patients' age (≤ 50 years or > 50 years), both in UF cc and MFMC cc groups, yielded a statistically significant relative risk of 1.42, showing that age is a risk factor, similar with other studies in the literature [22].

Numerous studies showed that survival decreases with the increase of the tumor size [23-25]. Takeuchi et al. showed that at 7.5 years, only tumor size and lymphovascular invasion had a significant effect on survival in multivariate analysis [26]. In our study, survival was inversely proportional with T status: the larger the tumor was, the lower the 5 and 10-year survival in both the UF cc and MFMC cc groups, but with statistically significant differences only in 10-year survival rates (T1: P = 0.05, T2: P = 0.04, T3: P = 0.04). The same results were obtained by Boyages et al.: in tumors with a maximum size over 2 cm, survival at 10 years

Table 6. Studies analyzing overall survival at 5 and at 10 years in UF and MFMC carcinomas of the breast

Authors	Number of cases analyzed	5-year OS (%)		10-year OS (%)		*p*-value
		UF cc	MFMC cc	UF cc	MFMC cc	
Yerushalmi et al. [9]	25.320	85.9	85.4	70.2	68.4	N/A
Litton et al. [19]	300	69.7	67.3	N/A		0.7
Dabakuyo et al. [16]	4.223	77	68	62	52	0.002
Ustaalioglu et al. [20]	697	94.5	90.2	N/A		0.1
Boyages et al. [17]	848	NA 88.1 (Tu ≤ 2 cm)		72.1 (Tu > 2 cm)	54.7 (Tu > 2 cm)	0.002
				87.9 (Tu ≤ 2 cm)		0.837

Abbreviation: Tu-tumor focus size.

was 54.7% in MFMC cc and 72.1% in UF cc (P = 0.008), influence that persisted in the multivariate analysis (RR=1.91, p-0.012), after a mean follow-up period of 10.4 years [17].

The 5-survival rate in our study was 83.3% (MFMC cc) and 83.3% (in UF cc) in patients without metastases (P = 0.68), opposed to 53.2% (in MFMC cc) and 54.5% (in UF cc) in patients with metastases (P = 0.98), in accordance with the results of Fisher et al. [27], who demonstrated that survival at 5 years in patients without axillary metastases was 82.8%, compared to 73% (in patients with 1-3 positive axillary lymph nodes), 45.7% in patients with 4-10 positive lymph nodes and only 28.4% in patients with more than 10 positive lymph nodes [27].

Focality was found to be a poor survival prognostic factor in our analysis, with higher mortality rates, much lower 5 and 10-year survival rates and reduced median survival compared to UF cc. However, multivariate analysis of several prognostic factors (age, tumor size, lymph node status and focality) have shown in this study that focality is not an independent prognostic factor in relation to survival, as opposed to tumor size and axillary lymph node status. Lynch et al. concluded in a multivariate analysis that MFMC cc did not have an independent impact on recurrence free survival, breast cancer specific survival or overall survival [6]. Different other 4 studies considered multifocality as an independent prognostic factor [4, 5, 16, 20].

While most studies show an increased rate of lymph node metastases in MFMC cc vs. UF cc, the data regarding the influence of focality on the prognosis are dichotomy (**Table 7**).

A recent systematic review and meta-analysis that studied the effect of MFMC cc on the outcome in early breast cancer concluded that multifocality appears to be associated with a worse prognosis, however, substantial inter-study heterogeneity limits the precise determination of the increased risk. Further validation of the independent prognostic impact of multifocality is warranted [21].

The differences in data concerning survival in multiple breast carcinomas could be caused by many factors, such as: case inclusion criteria, variations in the definitions used, different statistical analysis methods and different interpretations. At the same time, there is no standard method in multiple carcinoma surgical management and treatment, and thus it is difficult to compare studies concerning survival.

Although regarding staging and treatment, AJCC 2010 [34] and TNM 2012 [10] recommend assessing only the largest tumor focus, in general, patients with MFMC cc undergo more aggressive surgical treatment, such as total mastectomy, even in early stage carcinomas [35]. Since these cases are associated to a higher extent with axillary lymph node metastases (in which case chemotherapy is recommended), they also benefit more from adjuvant chemotherapy than patients with UF cc. These could be partial explanations of the absence of statistically significant differences in MFMC cc survival compared to UF cc.

In this study, multifocality in breast carcinoma was associated with higher mortality rates, a

Table 7. Studies regarding the prognostic significance of the presence of multiple foci in breast carcinoma (MFMC vs. UF)

Authors	Survival indicators
Worse prognosis	
Egan, 1982 [15]	Mortality ↑
Dabakuyo, 2008 [16]	Mortality ↑
	5 and 10-year survival ↓
Yerushalmi, 2009 [9]	Survival rate slightly ↓
Boyages, 2010 [17]	Mortality rate ↑
	5 and 10-year survival ↓
Weissenbacher, 2010 [4]	Mean survival ↑
	↑ Local recurrence rate
	↑ rate of distant metastases
Tot, 2011 [5]	↑ risk of death due to breast carcinoma
Ustaalioglu, 2012 [20]	↓ Disease free survival
Wolters, 2013 [28]	↓ Recurrence free survival
Pekar, 2013 [29]	↓ Breast Cancer Specific Survival
No influence on prognosis (no statistically significant differences between compared groups)	
Vlastos, 2000 [30]	Breast Cancer Specific Survival at 10 years
	Disease-Free Survival
Middleton, 2002 [31]	Disease-Free Survival at 5 and 10 years
Oh, 2006 [32]	Overal Survival at 5 years
Litton, 2007 [19]	Overal Survival, Relapse-Free Survival
Joergensen, 2008 [11]	Overal Survival
Cabioglu, 2009 [33]	Disease-Free Survival at 5 years
Rezo, 2011 [7]	Overal Survival, Progression Free Survival
Lynch, 2012 [6]	Relapse-Free Survival, Breast Cancer Specific Survival-worse prognosis at 5 years (only in UVA, not in MVA-other factors are associated with ↓ survival rates

Abbreviations: UVA - univariate analysis, MVA - multivariate analysis.

lower overall survival at 5 years and at 10 years, yielded a lower median survival, but did not constitute an independent prognostic factor in multivariate analysis. However, since data concerning 10-year survival rates in relation with tumor size show statistically significant differences between unifocal and multiple carcinomas and by Cox regression analysis, survival is independently influenced by T status (advanced T status, unfavorable as shown in this study), an estimation of the overall tumor burden in multiple tumors should be reported, as it might have an influence on which protocol is being selected for treatment. We stress the necessity of multiple future prospective studies, based on uniform definitions and inclusion criteria of cases that benefit from similar oncologic treatment, since the results of these future studies could have an impact on current AJCC and TNM staging systems.

Disclosure of conflict of interest

None.

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