

ANALYSIS OF THE PROGNOSTIC ROLE OF THE NUMBER OF CANCER FOCI IN BULGARIAN PATIENTS WITH MULTIPLE BREAST CANCER

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Abstract

Ipsilateral synchronous primary multiple breast cancer (MBC) is a relatively unknown subject compared to unifocal breast cancer (UBC) and includes the group of multifocal (MFBCs) and multicentric BC (MCBC). The aim of our research is to evaluate the prognostic value of the number of cancer lesions for overall survival (OS) and local recurrence-free survival (LFS) in Bulgarian patients with MBC and UBC. A retrospective study was conducted over 685 Bulgarian women with BC, diagnosed and treated for a period of ten years (March 2009 – March 2019) at the Department of Surgery, University Hospital “Tsaritsa Yoanna – ISUL”, Medical University of Sofia. The results from dividing the patients into two main groups according to the number of primary lesions showed that cases diagnosed with UBC were 513 (74.9%) and the ones with MBC – 172 (25.1%). The largest subgroup included females with 2 to 3 tumours ($n = 134$, 78%), followed by cases with 4 to 6 lesions ($n = 35$, 20.3%) and women with 6 to 8 foci ($n = 3$, 1.7%). The statistical analysis of OS showed significant difference between the two main groups UBC and MBC, $p = 0.003$. When comparing the subgroups of patients with MBC according to the absolute number of multiple foci we also established differences in OS even though with no significant value, $p = 0.570$. Statistical analysis of LFS among patients with different number of synchronous cancer foci reports significant difference – $p = 0.041$. MBC unites various lesions with different clinical manifestation, histopathological characteristics and more aggressive prognosis in comparison with UBC.

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Key words: multiple synchronous ipsilateral breast cancer, unifocal breast cancer, prognosis

Introduction. Breast cancer (BC) is the most common oncological disease in females worldwide with approximately 2.3 million new cases in 2020 [1]. BC continues to represent the leading cause of death from malignant tumour in Bulgarian patients.

Additional tumour foci in the same breast distant from the original cancer were initially described in BC cases in 1920 by CHEATLE [2]. Gradually the topic of numerous cancer lesions became an intriguing area, which is more frequently addressed in the last 30 years [3].

Ipsilateral synchronous primary multiple BC (MBC) is a relatively unknown subject compared to unifocal BCs (UBCs) and includes the group of multifocal (MFBC) and multicentric BC (MCBC). MBC represents a heterogenous disease which varies widely regarding its biological features, aggressiveness and clinico-pathological characteristics in different patients (intertumour heterogeneity) and in separate tumours as well (intratumour heterogeneity).

The cited incidence of MBC according to different sources varies between 5 and 44%. The difference in the documented results could be explained by several factors: choice of definition, specificity of histo-pathological assessment and sensitivity of the particular imaging tool used for diagnosis [4–6].

Series of studies prove the negative prognostic role of plural BC foci, which are associated with higher rate of local recurrence (LR) [7–9]. Many authors find correlation between multiple tumours and positive nodal status, pointing it as a sign of more aggressive biological behavior [10–12].

The aim of our research is to evaluate the prognostic value of the number of cancer lesions for overall survival (OS) and local recurrence-free survival (LFS) in Bulgarian patients with MBC and UBC.

Material and methods. A retrospective study was conducted over 685 Bulgarian women with BC, diagnosed and treated for a period of ten years (March 2009 – March 2019) at the Department of Surgery, University Hospital “Tsaritsa Yoanna – ISUL”, Medical University of Sofia. The design of the study was based on the following criteria: 1. Histological and immunohistochemical verification of the type and number of all primary synchronous cancer lesions; 2. Full report of data (clinical, imaging and laboratory tests), necessary for the correct assessment of OS and LFS for the 10-year follow-up period.

For the aim of the investigation the cohort of 685 patients were divided into two main groups according to the number of tumour foci – the first group of patients with diagnosed UBC, and the second one with MBC. The last one was further classified into three subgroups: women with 2 to 3, 4 to 6, and 6 to 8 multiple cancers in the same breast.

TNM Classification of Malignant Tumours was used for the disease staging [13] with the addition of American Joint Committee on Cancer (AJCC) criteria. Obtaining the data for the estimation of OS and LFS was made possible due to the predetermined schedule for a strict follow-up, official record from National Cancer Registry and CRAS (The Civil Registration and Administrative Services).

Statistical package SPSS 17.0.1. was used for data analysis. The significance level $p < 0.05$ was chosen for rejecting the null hypothesis.

Results. The estimated median age at diagnosis for all patients was 56.5 years – 57.6 for the women diagnosed with UBC and 53.6 for MBC cases. The youngest patient with UBC was 24 years old and the oldest – 103 years old. In comparison the lowest age at diagnosis for the group of MBC cases was 24 years and the highest – 84 years.

The results from dividing the patients into two main groups according to the number of primary lesions showed that cases diagnosed with UBC were 513 (74.9%) and the ones with MBC – 172 (25.1%). The largest subgroup included females with 2 to 3 tumours ($n = 134$, 78%), followed by cases with 4 to 6 lesions ($n = 35$, 20.3%) and women with 6 to 8 foci ($n = 3$, 1.7 %). It was found that cases with MCBC dominated in the population of patients with number of synchronous cancers > 4 ($n = 21$, 60%).

We found ten cases (5.8%) with a histological discordance between the largest primary cancer and the additional foci. The most frequent example of histological heterogeneity was represented by invasive ductal carcinoma in combination with invasive lobular carcinoma ($n = 3$, 1.7%). In the remaining cases the additional invasive carcinomas were defined as papillary ($n = 2$, 1.16%), mucinous ($n = 2$, 1.16%), tubular ($n = 1$, 0.58%) and coloid ($n = 1$, 0.58%). In one patient we have observed an absolute histological distinction between the examined foci with invasive ductal, invasive lobular and invasive papillary carcinoma present.

The statistical analysis of OS showed significant difference between the two main groups UBC and MBC, $p = 0.003$. The relative part of patients with MBC ($n = 172$) who survived the first 5 years after the surgical treatment was demonstratively lower – 85.1% than the compared one of patients with UBC ($n = 513$) – 94.7%. For a period of 10 years the OS has gradually reduced to 69.3% for the MBC group and to 86.5% for the group of UBC.

The summarized results are shown in Fig. 1 and Table 1.

The median survival time was equal to 8.88 years (95% CI, from 8.34 to 9.42 years) for the analyzed cases with MBC compared to 9.56 years (95% CI, from 9.35 to 9.76 years) for the control cohort of patients with UBC.

When comparing the subgroups of patients with MBC according to the absolute the number of multiple foci we also established differences in OS even though with no significant value, $p = 0.570$. Patients with 2–3 foci had median survival time of 9.09 years (95% CI, from 8.50 to 9.68 years). For the second subgroup of patients (cases with 4–6 tumours) the median survival time is 8.56 years (95% CI,

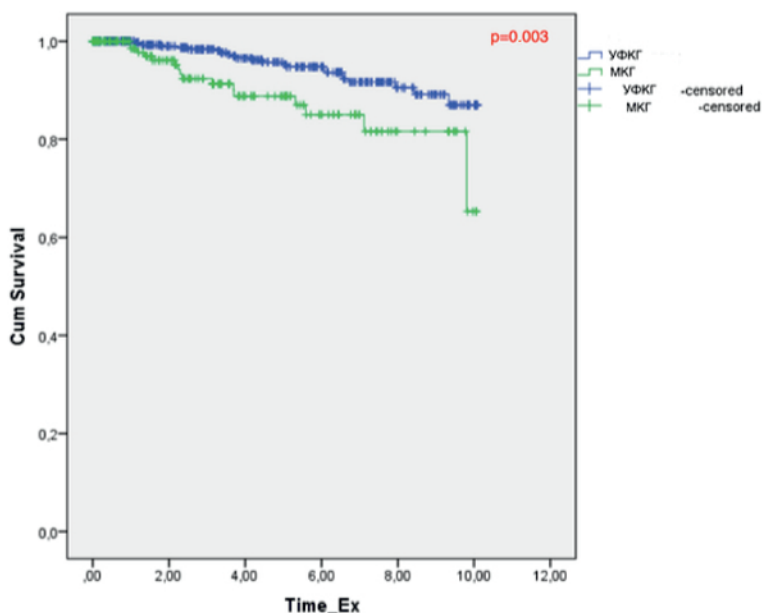


Fig. 1. OS for patients with MBC ($n = 172$) and UBC ($n = 513$), $p = 0.003$

T a b l e 1

Relative part of patients with MBC ($n = 172$)
and UBC ($n = 513$) with OS – 5 and 10 years

Group	Period (years)	OS (%)
MBC ($n = 172$)	5	85.1
	10	69.3
UBC ($n = 513$)	5	94.7
	10	86.5

from 7.21 to 9.91 years) and patients with the highest number of cancers (over 6) had median survival time equal to 8.06 years (95% CI, from 6.42 to 9.70 years).

The results are illustrated in Fig. 2.

Statistical analysis of LFS among patients with different number of synchronous cancer foci reports significant difference – $p = 0.041$. In patients with most tumours the median survival rate without LR is 7.47 years (95% CI, from 5.76 to 9.18 years), while in patients with least number of tumours – 9.53 years (95% CI, from 9.09 to 9.98 years). The value of the analyzed index for patients with 4–6 lesions is 9.23 years (95% CI, from 8.15 to 10.32 years) (Fig. 3).

Discussion. The question of the different origin of multiple breast cancer lesions remains controversial. It is not clear yet if the multiple foci arise separately or as metastatic deposits of one single primary cancer. The monoclonal origin suggests that isolated tumours must be perceived as intramammary metastases, characterized with more invasive abilities compared to the unifocal cancer. This

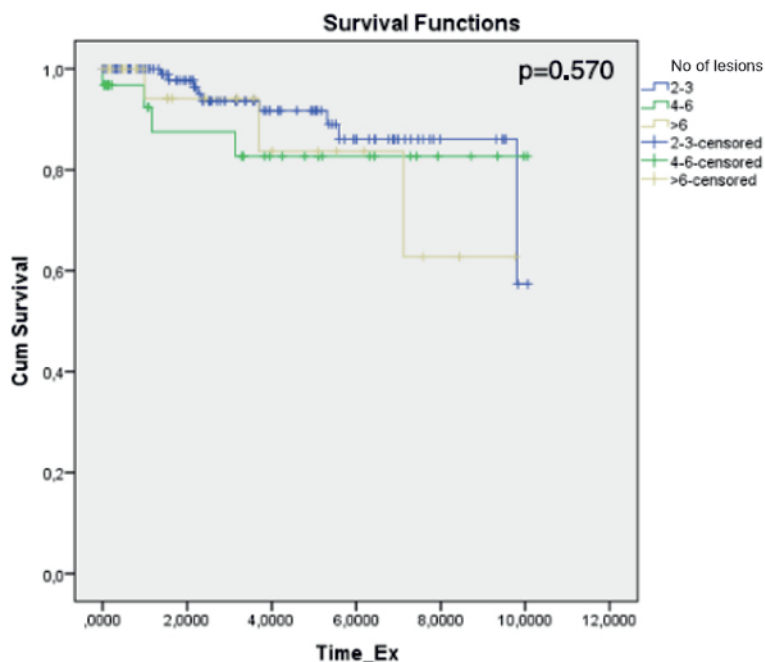


Fig. 2. OS in patients with MBC ($n = 172$), according to the number of lesions, $p = 0.570$

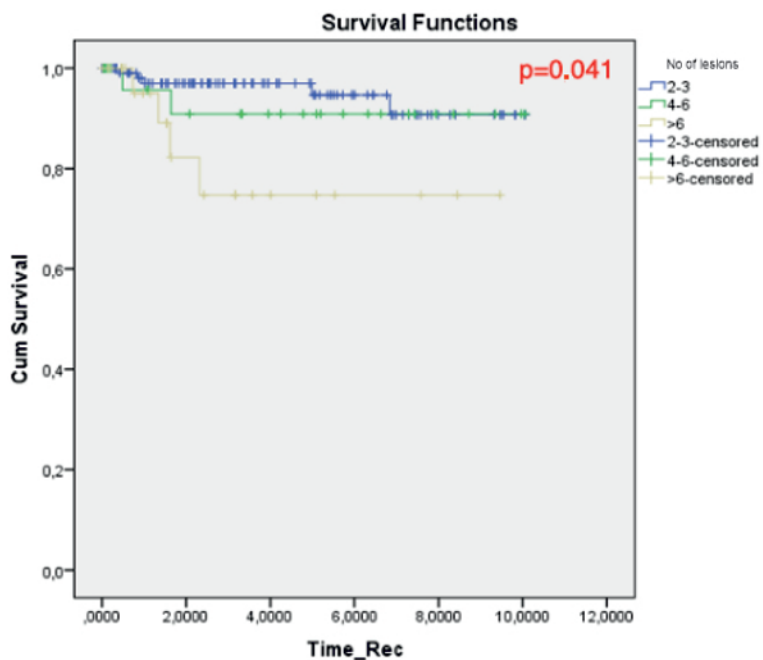


Fig. 3. LFS in patients with MBC ($n = 172$), according to the number of lesions, $p = 0.041$

conclusion stimulated WEISSENBACHER et al. [14] to focus their attention to the expression of glycoproteins, associated with cell adhesion. Results from the study confirm the more aggressive biological behaviour of MBC through down-regulation of E-cadherin. PEKAR et al. [15] emphasized on the prognostic and therapeutic value of interlesional heterogeneity, registered in 14.6% of cases in regard to grading and 5.5% in regard to tumour subtype in analysis of 110 patients. Females with documented phenotypic heterogeneity are with proven worse prognosis.

We have not found a reported case of an absolute histological discordance between all cancer foci in the available literature so far as the one we have observed with three different types of invasive carcinoma (ductal, lobular papillary).

The results from the comparative analysis between the main groups in regard to OS show almost complete concurrence with the ones in the study of VLASTOS et al. [16] – 92% on the fifth year and 84% on the tenth for cases with UBC. Our results for OS are close to the results of YERUSHALMI et al. [17], who studied 25 230 women with MBC 85.4% and 68.4%, respectively, on the 5th and 10th year of follow-up. The data is similar to the reported by OH et al. [18] for 5-year OS – 86% in cases with MBC and to the analysis of USTAALIOGLU et al. [19] for the same parameter – 94.5% for patients with UBC and 90.2% for patients with MBC. Cases with neoadjuvant chemotherapy were excluded from the last research because of the worse reported prognosis. The results for median survival time in our patients with single cancer are close to the announced value by BOROS et al. [20] – 10.5 years. They have estimated far lower median survival time for MBC cases – 6.5 years.

When evaluating the influence of the number of synchronous lesions over the prognosis we have found that patients with more tumours (6–8) have shorter median survival time than those with just 2–3 tumours – 8.06 years versus 9.09. CHUNG et al. [8] documented that bigger number of carcinomas is associated with higher rates of LR and lower OS. The results are similar to the ones from Weissenbacher et al. [14] and Ustaalioglu et al. [19]. The number of cancer foci is significant regarding LFS ($p = 0.041$), as our study points. In patients with more than 6 tumours the median survival rate without LR is the shortest – 7.47 years and in patients with 2–3 tumours – the longest (9.53 years). We must assert that the type of surgical treatment does not influence the statistical analysis because women with MCBC were indicated only for mastectomy, while patients with MFBC were suitable for BCS or mastectomy following the generally accepted recommendations for MBC treatment.

Accurate clinical evaluation of BC patients' prognosis in cases with more than one cancer is crucial for making correct decisions regarding the precise type of adjuvant therapy. The advance of industrial pharmacy in drug development could lower the risk of LR in these cases.

Conclusion. Ipsilateral synchronous primary MBC including MCBC and MFBC represents a specific heterogeneous subgroup of BC with unknown biology

and pathogenesis. It unites various lesions with different clinical manifestation, histopathological characteristics and more aggressive prognosis in comparison with UBC.

Our research over 685 Bulgarian patients with BC demonstrates significantly lower OS for those with MBC ($p = 0.003$). The number of primary cancer foci appears essential for LFS ($p = 0.041$), but does not play a significant role in OS ($p = 0.570$). The peculiarity of MBC as a pathology sets series of unsettled problems in diagnostic and therapeutic aspect on a large scale. Unacquainted additional tumours during medical imaging diagnosis lead to incorrectly defining the disease as unifocal. The reasons behind these diagnostic gaps could be found in imperfection of the chosen imaging modality and lack of knowledge regarding MBC.

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