HETEROGENEITY IN MULTIPLE BREAST CARCINOMAS: THERAPEUTIC AND PROGNOSTIC IMPLICATIONS

Breast carcinoma is the most frequent form of cancer in women, with an estimated prevalence of 3,763,070 cases in Europe in 2010. At the same time, breast carcinoma is the main cause of cancer mortality in women in the European Union. Most of these tumors are unifocal, while a variable proportion are multiple (multifocal and multicentric) breast carcinomas.

There are no published studies on the incidence of multiple carcinomas in Romania (0 PubMed citations). On the other hand, the method of breast specimen sampling is not standardized, and each department uses a different method of sampling and defining multiple lesions. In the first study, after analyzing and comparing the two methods of breast specimen sampling used in the Tîrgu-Mureş University Center (the traditional/classic method and the modern/multidisciplinary team method), I found that the incidence of multiple breast carcinoma in Tîrgu-Mureş was significantly higher between 2007 and 2012 compared to 2002-2006 (31.04% versus 13.31%), ($p<0.0001$), after introducing the modern method.

Regarding tumor size in breast carcinoma, its assessment is problematic because most of the time this tumors have highly irregular shape and the largest diameter assessed by the pathologist only seldom indicates their real size. The possibility of assessing tumor size erroneously is higher in multiple carcinomas. AJCC 2010/ TNM 2012 recommend using the maximum diameter of the largest tumor focus in multiple carcinomas and only mentioning the presence of multiple foci between parentheses, even if gross multiple foci are often visible. The diameter of secondary foci is not reported. In these cases, tumor diameter and even volume may be underestimated, which influences the risk of local recurrence and reduces survival. The aim of the second study was to determine the best method of assessing tumor size in multiple breast carcinomas in correlation with axillary lymph node metastases, and the results showed that multiple breast carcinoma foci have different biological features, with an increased potential of generating axillary metastases. The use of the aggregate diameter, however, is not correlated with a higher rate of axillary metastases, and therefore it should not be used in the TNM staging of multifocal/ multicentric carcinomas.

Multiple tumor foci can be, according to various studies, microscopically and clonally heterogeneous (polyclonal), but other studies state the contrary and uphold the monoclonal theory, stating also that most of these foci are morphologically identical. CAP recommends reporting only the morphological features (histological type and grade) of the largest invasive tumor focus in multifocal/multicentric carcinomas; in cases in which any of the additional tumor foci is different, this should be reported in the "Comments" section, and the features of these additional foci (size, microscopic type, microscopic grade) should be reported only as additional information. The systemic adjuvant therapy in multiple breast carcinoma is based upon the morphological features of the largest tumor focus, and does not take into account simultaneous multiple foci. In the third study, aimed at assessing whether multiple tumor foci are morphologically homogenous or heterogeneous, I found that multiple foci display an important morphological heterogeneity. Intertumoral heterogeneity in tumor type and grade was detected in 15 of 91 tumors (12.08%) and in 9 of 91 tumors (9.89%), respectively. Because tumors known to have a good prognosis and a low histological grade were encountered in association with

simultaneous foci known to have a poor prognosis and a higher histological grade, it is my opinion that it is imperative to report the size, histological type and grade of every tumor focus. By only reporting the morphological features of the main (index) tumor, the chance for the patients to benefit from an adequate oncological therapy may be diminished. I think that this type of study, together with studies on clonality, should involve larger populations, in which the probability of diagnosing multiple carcinomas with differing morphological features may be higher.

Because one of the most important prognostic factors in breast carcinoma is the presence of axillary lymph node metastases, the aim of the 4th study was to determine the prognostic significance of the presence of multiple tumor foci in breast carcinoma versus unifocal carcinoma, in correlation with axillary lymph node metastases. I found that axillary lymph node metastases appear in a higher percentage in multiple carcinomas versus unifocal carcinomas (69.17% versus 59.16%) ($p=0.052$). The rate of producing axillary lymph node metastases increased with tumor size.

In multiple carcinomas, between 3% and 37.5% of cases may display different histological type and/or grade, according to data in the literature. I have not found publications regarding the influence of the histological features of multiple foci on the morphological appearance of axillary lymph node metastases (0 PubMed citations), which led to the idea of the fifth study: assessing the histological features of axillary lymph node metastases and correlating it with the histological and biological features of individual tumor foci in multiple breast carcinomas. I found that the morphological features of the axillary lymph node metastases in multiple carcinomas are in most cases similar to those of the tumor focus that displays the most aggressive histological type/highest histological grade, which is not necessarily the largest focus. For this reason, in my opinion, it is required to assess and report each tumor focus of multiple carcinomas independently.

International therapeutic guidelines recommend adjuvant endocrine therapy in patients with hormone-sensitive breast carcinoma that expresses estrogen receptors (ER) and/or progesterone receptors (PR), and anti-HER2 therapy in HER2-positive cases. High proliferation index (Ki67), high histological grad and ER/PR negativity are factors that indicate chemotherapy. European guidelines recommend, in multiple breast carcinomas, that these biological parameters (ER, PR, Ki67 and HER2) should only be assessed in the largest tumor focus (index or main tumor); additional tumor foci should be assessed only when they differ morphologically from the main tumor (CAP guidelines). The sixth study aimed to perform a morphologic and immunohistochemical (molecular) analysis of all multiple foci tumor, and to record all concordances/mismatches among them. Out of the 155 MFMC carcinomas analyzed, with a total of 463 tumor foci, I found mismatches in 11.61%- 29.03% of the cases, depending on the analyzed parameter, and histological type mismatches in 14.83% of the cases. 19 patients (12.25%) did not benefit from adequate oncological therapy. This study underlines the importance of assessing and reporting each tumor focus in multiple breast carcinomas independently, regardless of their concordant/discordant morphology.

Multifocality is not listed among the “traditional” prognostic factors (tumor size, histological grade, axillary lymph node status) or among second generation ones (ER, PR, Ki67 index and HER2 status) in breast carcinoma. Since data available in literature on the influence of multifocality on the prognosis are

divergent, the aim of the seventh study was to analyze survival in multiple breast carcinomas compared to unifocal ones. The results show that multifocality in breast carcinoma is associated with a lower general survival at 5 years and at 10 years, a higher mortality rate and a lower median survival, but it is not an independent prognostic factor in multivariate analysis.

I believe that, after analyzing all these aspects, supplemental information concerning the management and prognosis of multiple carcinomas can be obtained, with important practical implications. These implications are aimed especially at including this new informations in future editions of European and American breast carcinoma diagnostic and therapeutic guidelines, and also at improving prognosis in breast carcinomas.

Keywords: multiple breast carcinomas, multifocal, multicentric, prognosis, management, survival

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