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Archives of Cancer Biology and Therapy Short Communication

Prognosis and Survival of Medullary Carcinoma of the Breast

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Medullary breast carcinoma (MBC) is a rare tumor, representing 3% to 5% of invasive breast carcinomas [1,2]. The World Health Organization defines it as a well-circumscribed invasive tumor, composed of poorly differentiated cells, arranged in sheets, without gland formation and a scarce collagen stroma with the presence of a very prominent lymphoplasmacytic infiltrate [3]. In 1977 Ridolfi et al. [4] proposed five specific histopathological criteria for diagnosis: well-circumscribed tumor, syncytial architecture in al less than 75% of the areas examined, diffuse stromal infiltration with lymphocytes and plasma cells, absence of tubular differentiation and/or intraductal component, that is, forms of glandular patterns, and moderate or marked anisonucleosis.

Research by Wang et al. [5] revealed that MBC have unique clinicopathological characteristics, including an earlier age at diagnosis, a higher grade, a more advanced stage, and a larger tumor size.

Intense lymphoid infiltration makes MBC an attractive subject for detailed studies regarding the development of new immunological approaches for cancer treatment [6]. In this regard, Kuroda et al. [7] investigating the infiltration immunophenotype Lymphocytic disease in MBC found very few NK cells (according to CD56 antibody reactivity). However, there was a significantly higher percentage of CD3, CD8, TIA-1 and granzyme B lymphocytes infiltrating the tumor stroma. In addition, there are more CD8-positive than CD4-positive T-cell lymphocytes within the tumor cell nests, unlike the proportions found in ductal carcinoma.

Another relevant and interesting aspect is that most MBCs are characterized by the negative expression of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) [8], by which is called this subtype of breast carcinoma, triple negative [9]. In this regard, Piamo et al. [10] in a 9-year investigation, found that 88.9% of tumors do not express hormone receptors (ER and PR) and Her-2. Similar to that obtained by Aksoy et al. [11] (91.5% triple negative). However, in the study by Martinez et al. [12] the 56.8 and 58.4% were ER and PR-negative, respectively.

It is known that triple negative breast cancer is often relevant for a worse prognosis. However, although patients with MBC show aggressive histological characteristics, there is no consensus regarding the difference in clinicopathological characteristics and results between MBC and invasive ductal carcinoma (IDC).

There is a postulate that the extensive presence of plasma cells and lymphocytes prevents it from growing and spreading rapidly, as described by Zangouri et al. [13] whose results show that less local invasion occurs in MBC compared to IDC ($p<0.001$).

In this sense, some studies have revealed that the histology of MBC is associated with a favorable prognosis [1,4,14-16]. Other studies do not confirm this conclusion and even indicate that the prognosis of MBC does not differ from CDI [17,18].

Therefore, this brief note is intended to comment on the prognosis and survival of medullary breast carcinoma and thereby motivate new and necessary research in this field, since the determination of these factors is important to identify patients with greater risk of disease recurrence and death, these patients being able to benefit from more aggressive treatment.

Aksoy et al. [11] concluded that PR-negativity, atypical

Author	Overall survival
Khomsi et al. [21]	85% (5 years)
Khomsi et al. [21]	74 a 90% (lymph node-negative) (10 years)
Martinez et al. [12]	69,6% (Blacks) y 79,8% (White) (10 years)
Martinez et al. [12]	16,6% lower in >50 years, than in <50 years (10 years)
Aksoy et al. [11]	95,7% (5 years)
Dendale et al. [1]	81% (10 years)
Zangouri et al. [13]	98,1% (MBC) y 92,8% (CDI) (5 years)
Lim et al. [22]	97,5% (Tumors >2 cm in size) (5 years)

Table 1. Overall survival of patients with medullary breast carcinoma.

histopathological evaluation, absence of lymphovascular invasion, smaller tumor, and inferior lymph node involvement are favorable prognostic factors ($p<0.05$). However, none of these factors were determined to be significant independent prognostic factors for overall survival (OS) ($p>0.05$).

Martinez et al. [12] identified that a positive ER state predicts a worse prognosis ($P=0.003$); while PR-positive patients have a survival benefit ($P=0.002$).

According to Dendale et al. [1] the accumulation of p53 protein, which is found in most MBC, is not related to the clinical outcome, that is, p53 status is not predictive of survival or of distant or local recurrences. But the pathological involvement of the axillary nodes if they are factors that predict the result.

A totally interesting aspect of MBC is its association with mutations in the BRCA1 gene. Among the multiple functions of this gene is its role in DNA repair mechanisms and the maintenance of genomic stability opens new therapeutic possibilities [19].

Approximately 13% of BRCA1 tumors have pure marrow histology and 60% of BRCA1 tumors have some marrow features. The study by Lakhani et al. [20] who compared 114 BRCA1-mutated tumors with a large number of controls; found 3 characteristics independently associated with BRCA1 mutations: high mitotic count, lymphocytic infiltrate, and thrust margins.

Regarding survival (Table 1), Khomsi et al. [21] found a 5-year relapse-free overall survival (OS) rate of 85% in patients with MBC.

In patients with negative lymph nodes, the 10-year OS rate is 74% to 90% [21]. This corresponds to what was found by Martinez et al. [12] who stated that lymph node involvement significantly reduces overall survival.

Regarding the relationship between survival with age and skin color, Martinez et al. [12] described that in patients> 50 years of age, 10-year survival is 16.6% lower than that of patients <50 years ($p<0.001$); and the 10-year survival for blacks is 69.6% compared to 79.8% for whites.

In the investigation by Aksoy et al. [11] a 5-year recurrence-free survival rate of 87.4% and an overall survival rate (OS) of 95.7% were calculated. Very similar to those reported by Dendale et al. [1] (10-year OS rates and metastasis-free survival of 81% and 81.4%, respectively). When comparing the accumulated incidences of death of 5 years between the IDC and MCB, Dai et al. [23] reported that this is higher in IDC than in MCB ($p<0.001$). The 5-year disease-free survival (DFS) and the 5-year OS in the Zangouri et al. [13] investigation differed significantly between the MBC and ICD groups (DFS: 94.2% vs 86.3%, $p=0.008$; OS: 98.1% vs 92.8%, $p=0.004$).

Huober et al. [8] compared patients with spinal tumors with those with ductal tumors in subgroups defined by lymph node status, and OS for the spinal category was better in all cases, significantly for the node-positive cohort. When a negative PR status was added to the characterization of the medullary cohort in patients with grade 3 ER-negative tumors, the result did not change.

In the study by Lim et al., [22] breast cancer-specific survival (BCSS) and OS in Group II (received adjuvant chemotherapy) (97.3% and 97.3%, respectively) were significantly better compared to those in Group I (did not receive adjuvant chemotherapy) (89.2% and 86.2%, respectively). In the subgroup analysis, in patients with tumors > 2 cm in size, those in group II had significantly better BCSS and OS (97.5% and 97.5%, respectively) compared to those in group I (78, 3% and 73.9%, respectively). In contrast, in those with tumors 1 to 2 cm in size, there were no significant differences in BCSS and OS between the groups (both 97.1% for group I and 95.2% and 92.9%, respectively, for group II). These findings are

consistent with what Aksoy et al. [11] stated about a better prognosis in a smaller tumor, as did Reinfuss et al. [24] who reported that tumor size affects overall survival.

These results not only confer a deeper understanding of MBC but also contribute to the practice of medical oncologists as clinical management and results are improved. Above all, the data regarding tumor size and its relationship with survival point to a more personalized therapeutic strategy in the sense of indicating less aggressive treatments in BC when these are smaller than 2 cm.

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