Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi 2025;12(2):155-160 *Orijinal Makale/Original Article*
Medical Journal of Mugla Sitki Kocman University 2025;12(2):155-160 *Tekin and Ünçel*
Doi: 10.47572/muskutd.1660645

Inflammation Tumor Microenvironment and Mast Cells in Breast Cancer

Meme Kanserinde İnflamasyon Tümör Mikroçevresi ve Mast Hücreleri

Leyla TEKİN, Melek ÜNÇEL

Mugla Training and Research Hospital, Department of Pathology Department, Mugla,Turkey

Öz

Tümör mikroçevresi fibroblastlar, endotel ve bağışıklık hücreleri ve hücre dışı matristen oluşur ve kanseri çevreler. Mast hücreleri, anjiyogenez, stroma immünomodülasyonu ve kanserlerde doku yeniden şekillenmesi ile ilişkilidir. Farklı tümörlerde, tümör mikroçevresine göre antitümör veya güçlendirici etkilere sahip olabilir. Meme kanseri stromasındaki bağışıklık hücreleri, kanser davranışını şekillendiren inflamatuar mikroçevreyi oluşturur. 2017-2020 yılları arasında meme kanseri nedeniyle mastektomi geçiren 85 kadın hastadan alınan örnekler retrospektif olarak değerlendirildi. Hematoksilen-eozin boyalı slaytlar temelinde immünohistokimyasal boyama yapıldı. Mast hücre yoğunluğu, üç yüksek yoğunluklu alanda sayılarak hotspot yöntemi kullanılarak değerlendirildi. Hem tümör çevresi hem de tümör içi yoğunluklar ayrı ayrı kaydedildi ve ortalama sayımlar üç alandan hesaplandı. CD117 üç büyük büyütmede (400x) sayıldı ve tümör içi ve tümör çevresi hücreler ayırt edildi. Tümör içi fibrozis ve lenfositlerin varlığı puanlandı. Sonuçta; tümör çevresi mast hücre sayısı ER negatif olgular ve metastatik lenf nodu sayısı yüksek olgularda ortalamanın altında bulundu. Lobüler karsinom ile tümör içi mast hücre yoğunluğu arasında ters bir ilişki gözlendi. Ek olarak, tümör içi mast hücre yoğunluğu ile artmış tümör boyutu arasında anlamlı bir ters ilişki vardı. Ortalamanın altında tümör içi mast hücre sayısına sahip vakalar, ER negatifliği, yüksek Ki67 proliferasyon indeksi, luminal grup vakaları ve fibrozis yokluğu ile anlamlı bir şekilde ilişkiliydi. Tümörlerde düşük mast hücre sayısı, zayıf prognostik parametrelerle ilişkili bulundu.

Anahtar Kelimeler: Mast Hücreleri, CD117, Meme Karsinomu

Abstract

The tumor microenvironment consists of fibroblasts, endothelial and immune cells, and extracellular matrix and envelops the cancer. Mast cells are associated with angiogenesis, immunomodulation of the stroma, and tissue remodeling in cancers. In different tumors, it may have antitumor or potentiating effects in relation to the tumor microenvironment. Immune cells in breast cancer stroma form the inflammatory microenvironment that shapes cancer behavior. Samples taken from 85 female patients who underwent mastectomy due to breast cancer between 2017 and 2020 were evaluated retrospectively. Immunohistochemical staining was performed on the basis of hematoxylin-eosin stained slides. Mast cell density was assessed using the hot-spot method, counting in three high-density areas. Both peritumoral and intratumoral densities were recorded separately, and average counts were calculated from the three fields. CD117 was counted at three high magnifications (400x), and intratumoral and peritumoral cells were distinguished. The presence of intratumoral fibrosis and lymphocytes was scored . Peritumoral mast cell count was found to be below average in ER-negative cases and in cases with high metastatic lymph node count. An inverse relationship was observed between lobular carcinoma and intratumoral mast cell density. In addition, there was a significant inverse relationship between intratumoral mast cell density and increased tumor size. Cases with below average intratumoral mast cell count were significantly associated with ER negativity, high Ki67 proliferation index, , luminal group cases and absence of fibrosis. Low mast cell count in tumors was found to be associated with poor prognostic parameters.

Keywords: Mast Cells, CD117, Breast Carcinoma

Introduction

Inflammation is the process that protects the body against internal and external stimuli and provides tissue homeostasis. Although the inflammation initially has a protective effect when tissue is damaged, when it continues for a long time, they create a suitable microenvironment for tumor cells proliferation, invasion, angiogenesis and metastasis (1). The tumor microenvironment consists of fibroblasts, endothelial and immune cells, and extracellular matrix and envelops the cancer. Immune cells in breast cancer stroma form the inflammatory microenvironment that shapes cancer behavior (2,3). A relationship has been established between inflammation and several tumors, including gastric, colorectal, prostate, cervical, and hepatocellular cancers (4).

Mast cells, originating from bone marrow stem cells, bind to the c-KIT receptor, a type of transmembrane protein tyrosine kinase (5). When activated, mast cells secrete mediators from cytoplasmic granules that aid in tissue repair, wound healing, and angiogenesis.Mast cells are found in various organs, including the lungs, skin, heart, and digestive system, and are associated with several malignancies (6,7). Their roles in cancer are complex, as they may exhibit either antitumor or protumorigenic effects depending on the tumor microenvironment (8). The prognostic value of mast cells in breast cancer remains controversial, with some studies linking high mast cell density to poor prognosis (9), while others suggest a positive association with favorable outcomes (10,11). High mast cell density in peritumoral or intratumoral regions has been observed in various cancers, including thyroid, gastric, kidney, pancreatic, prostate cancers, and malignant melanomas (3,12,13).

	ORCID No
Leyla TEKİN	000-0003-1172-5536
Melek ÜNÇEL	0000-0002-0304-2682

Başvuru Tarihi / Received: 18.03.2025
Kabul Tarihi / Accepted : 29.07.2025

Adres / Correspondence : Leyla TEKİN
Mugla Training and Research Hospital, Department of Pathology Department, Mugla,Turkey
e-posta / e-mail : dr.ltekin@hotmail.com

Chronic inflammation is recognized as a mechanism that defends the body against disruptions to homeostasis (14). The long-term presence of immune cells in tissues can activate oxidative stress, cell cycle proteins, DNA repair mechanisms, and apoptosis (15,16). This persistent inflammation contributes to a microenvironment suitable for tumor cell proliferation, survival, invasion, migration, tissue remodeling, angiogenesis, and metastasis (1).

In this study, we compared prognostic parameters related to mast cell density in the tumor microenvironment and fibrosis in the tumor stroma.

Material and Method

We retrospectively evaluated specimens from 85 female patients who underwent mastectomy due to breast cancer between 2017 and 2020. Immunohistochemical staining was performed based on hematoxylin-eosin stained slides. Four-micron sections were taken from formalin-fixed, paraffin-embedded blocks, using CD117 as the primary antibody. The slides underwent heat-induced epitope retrieval with a pH 6.0 citrate solution for 30 minutes, followed by blocking endogenous peroxidase with 3% hydrogen peroxide for 5 minutes. The primary antibody (CD117) was applied, followed by chromogen. All immunohistochemical procedures were conducted using a Leica Bondmax autostainer, and microscopic evaluations were performed with an Olympus BX46 light microscope. Mast cell density was assessed by two independent pathologists using the hot-spot method, counting in three high-density areas (40x). Both peritumoral and intratumoral densities were recorded separately, and average counts were calculated from the three fields.

Prognostic determinants such as age, tumor histology, localization, size, lymph node status, estrogen receptor (ER), progesterone receptor (PR), cerbB2 receptor status, and Ki67 proliferation indices were documented. For ER and PR positivity, nuclear staining above 1% was considered positive, with staining intensity scored from 1 to 3 (17). The threshold for Ki67 was set at 14%. For cerbB2, positivity was determined based on a 10% staining threshold, with scores ranging from 0 to 3, and cases positive for FISH amplification were scored as 2. CD117 was counted at three high magnifications (400x) Figure, and intratumoral and peritumoral cells were distinguished (Figure 1). The presence of intratumoral fibrosis and lymphocytes was scored as 0, 1, 2, or 3.

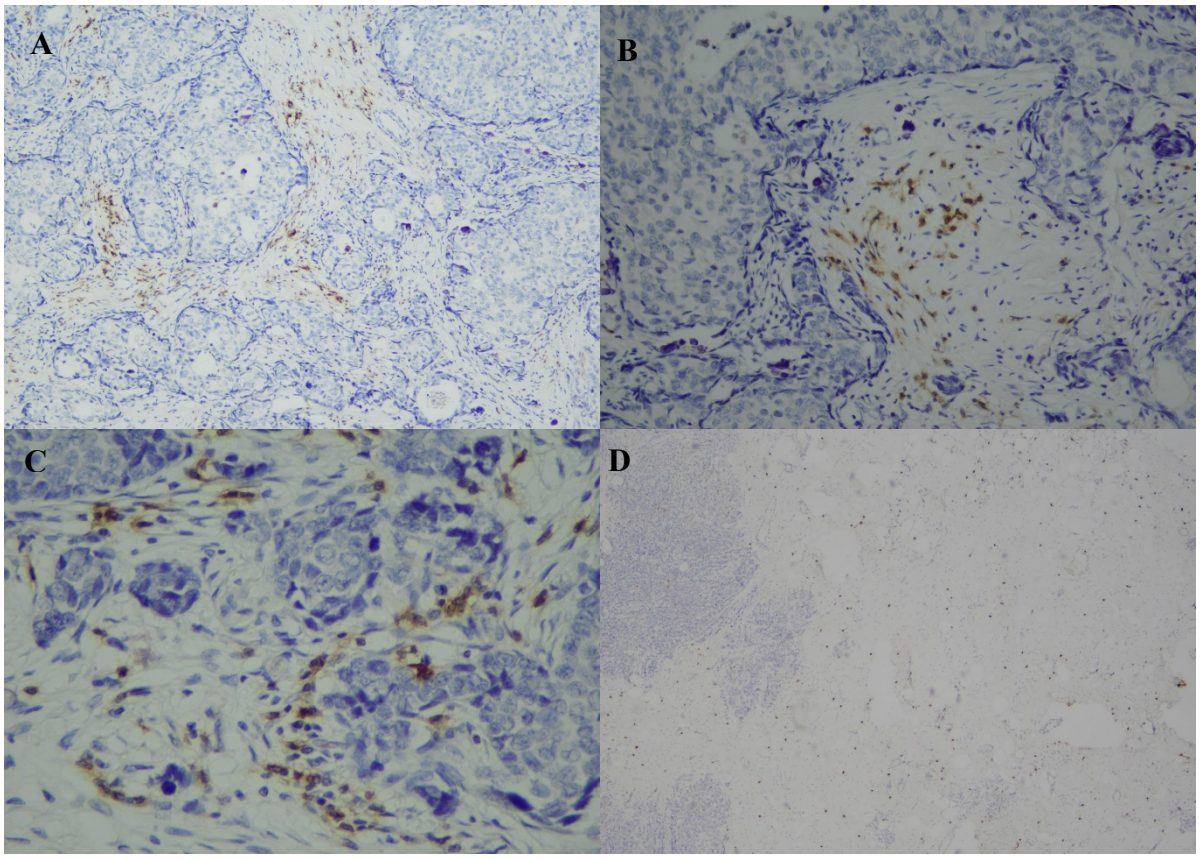

Figure 1. Intratumoral mast cell staining with CD117 immunohistochemistry A. X100 B. X200 C. X400 D. X40

Statistical Analysis

SPSS version 22 was used for statistical analyses. Survival evaluations were conducted with Kaplan-Meier analyses. Descriptive statistics are reported as median range with minimum and maximum values. Percentages are also presented with demonstrative tables. Variables were compared between two groups using the Mann–Whitney U test. Parameters with multiple groups were analyzed using the Chi-square method. Statistical significance was defined as a p-value ≤ 0.05.

Results

The study comprised 85 female patients aged 31 to 85, with a mean age of 54.9. According to the modified Bloom-Richardson grading system, 11 (12.9%) cases were grade 1, 59 (69.4%) were grade 2, and 15 (17.6%) were grade 3. Seventeen cases (20%) were ER negative, while 68 (80%) were ER positive. CerbB2 was positive in 9 cases (10.5%) and negative in 76 cases (89.5%). The Ki-67 proliferation index ranged from a minimum of 3 to a maximum of 50; 46 cases (54.1%) were below 14%, and 39 cases (45.9%) were above 14%. Tumor sizes ranged from 0.7 cm to 10 cm, with an average size of 2.5 cm. Lymph node involvement was absent in 48 cases (56.4%).

Table 1. Clinicopathological data

Characteristic	Number of cases	%
Age (31-85)	85	100
Tumor size		
pT1	31	36.4
pT2	38	44.7
pT3	16	18.8
Lymph node		
pN0	48	56.4
pN1	20	23.5
pN2	12	14.1
pN3	5	5.8
Nottingham grade		
G1	11	12.9
G2	59	69.4
G3	15	17.6
Histologycal type		
Ductal(NOS)	74	87
Lobular	11	12.9
Molecular subtype		
Luminal A	34	40
Luminal B	28	32.9
Luminal B HER2+	7	8.2
HER2+(Nonluminal)	2	2.3
Triple negative	14	16.4
Localization		
Unicentric	74	87
Multicentric	10	11.7
Bilateral	1	1.2
Lymphovascular invasion		
Yes	50	58.8
No	35	41.1

Molecular Subtypes:

- 34 cases (40%) were Luminal A
- 28 cases (32.9%) were Luminal B
- 2 cases (2.3%) were cerbB2 positive
- 14 cases (16.4%) were triple negative
- 7 cases (8.2%) were triple positive

CD117 counts ranged from 12 to 202 in the peritumoral area and from 0 to 135 in the intratumoral area. Perineural invasion was observed in 29 cases. Tumors were unifocal in 74 (87%) cases and multifocal in 11 (12.9%).

Peritumoral mast cell count below average correlated significantly with ER negativity and high lymph node metastasis status (N2-3) (p=0.068). An inverse relationship was observed between lobular carcinoma and intratumoral mast cell density. Additionally, intratumoral mast cell density was significantly inversely related to pT3 tumor status. Cases with below-average intratumoral mast cell counts were significantly associated with ER negativity, Ki67 indices above 14%, non-luminal group cases, and absence of fibrosis.

Clinicopathological data and histopathological parameters are presented in Tables 1 and 2.

Table 2. Histopathological parameters and their distribution

Characteristic	Number of cases	%
ER		
Positive	68	80
Negative	17	20
PR		
Positive	67	78.9
negative	18	21.1
CerbB2		
Positive	9	10.5
negative	76	89.5
Ki67		
≤	46	54.1
>	39	45.9
Fibrosis		
No	15	17.6
Low	42	49.4
High	28	32.9
Lymphocyte		
No	19	22.3
Low	40	47
High	26	30.5

Discussion

CD117 (also known as c-kit or stem cell growth factor receptor) is notably expressed in the luminal epithelial cells of normal adult breast tissue, as documented in previous studies (18). However, in our study, no expression of CD117 was observed in malignant breast tissue, which suggests a potential alteration or loss of this marker during the

transformation from normal to malignant breast cells. This observation raises important questions about the molecular changes that occur during the progression of breast cancer and the role that such alterations may play in tumor development or progression.

Breast cancer is one of the most common malignancies affecting women worldwide (19), and the relationship between inflammation and cancer outcomes has been extensively studied. Inflammation in the tumor microenvironment (TME) is known to have both antitumoral and protumorigenic effects, with the potential to influence the initiation, progression, and metastasis of tumors (14). It has been suggested that the presence of stromal mast cells in the tumor stroma may serve as an indicator of a more favorable prognosis in certain cancers, although the underlying mechanisms remain not fully understood (20). Mast cells, which are typically located in high density in the peritumoral area, particularly in the perivascular regions, have been shown to exhibit cytolytic activity against tumor cells in vitro, thereby potentially contributing to tumor growth inhibition (21). This points to a complex interaction where, under specific circumstances, mast cells may exert antitumoral effects by directly attacking cancer cells or by influencing other immune components in the TME.

At the same time, the role of mast cells in the TME is not entirely straightforward, as their presence can also support tumorigenesis. Studies have emphasized that inflammatory cells, including fibroblasts, lymphocytes, and mast cells, can play a critical role in promoting the initiation and progression of cancer, particularly through their influence on the stromal environment (22). Mast cells, especially in the early stages of tumor development, contribute to angiogenesis, the formation of new blood vessels, which is a crucial process for the growth and expansion of tumors (11, 23). Furthermore, mast cells are also implicated in promoting micrometastasis, which enhances the spread of cancer to distant sites, thus showing a protumorigenic effect during tumor progression. Several studies have also reported the frequent detection of mast cells in the neoplastic cell stroma, especially in proximity to vascular structures, which could facilitate the metastatic spread of tumor cells through the bloodstream (20, 24).

Additionally, the number of mast cells has been correlated with metastasis to regional lymph nodes, suggesting a role for these cells in promoting the spread of breast cancer to distant sites. Interestingly, the presence of mast cells has been reported to have prognostic significance, with some studies linking a higher density of peritumoral mast cells to poor outcomes, particularly with respect to lymphatic and perineural invasion, both of which are associated with worse prognoses (25). These findings indicate that while mast cells may play a dual role in the TME, their increased density, particularly in the peritumoral and intratumoral regions, could be linked to more aggressive tumor behavior. Indeed, the proteases secreted by mast cells in the TME have been shown to facilitate vascular invasion and the spread of cancer cells, further supporting the hypothesis that mast cells can be involved in metastasis and tumor progression (11, 23, 25).

Moreover, studies have found a positive correlation between the density of peritumoral mast cells and the histopathological grade of the tumor, suggesting that higher mast cell density may be a feature of more aggressive or poorly differentiated cancers (24). However, other studies report an inverse correlation between peritumoral mast cell density and tumor size, as well as a positive correlation with estrogen receptor (ER) positivity, indicating that the role of mast cells may be more complex and context-dependent. For instance, tumors that are estrogen receptor-positive (ER+) may exhibit different mast cell dynamics compared to estrogen receptor-negative (ER-) tumors, potentially reflecting less aggressive tumor biology (26).

Furthermore, some studies have reported a lack of significant correlation between mast cell density and tumor size, histological grade, or the status of ER/PR receptors, as well as HER2 overexpression, suggesting that mast cells may not always be reliable markers of tumor aggressiveness in early breast cancer (23,27). This points to the possibility that other factors in the TME, such as the presence of additional immune cells or stromal components, may influence the behavior of mast cells, modulating their effect on tumor progression in ways that are not immediately apparent from a simple correlation analysis.

There are also studies suggesting that both tumoral and peritumoral mast cell counts tend to be higher in grade 1 and grade 2 breast cancers (28), although a negative correlation has also been reported between mast cell numbers and Elston grading, which is used to assess the degree of differentiation in tumors (26). These conflicting results highlight the need for a more nuanced understanding of the role of mast cells in different tumor grades and the potential involvement of other molecular or cellular factors that may influence mast cell behavior in the TME.

Xiang et al. (29) have reported that peritumoral mast cell density was notably increased in cases of breast cancer with histological grade 3 tumors and in patients with lymph node metastasis, suggesting that mast cells might be involved in more aggressive forms of the disease. Similarly, Samoszuk (30) found that stromal mast cells were more prevalent in early-stage breast cancers, whereas intratumoral mast cells were more common in invasive tumors, further reinforcing the idea that mast cells can have

distinct roles at different stages of tumor progression.

In terms of molecular subtypes, it has been reported that the density of both intra- and peritumoral mast cells is generally higher in tumors that express high levels of hormone receptors, such as estrogen and progesterone receptors, which are typically associated with lower aggressiveness (23). This suggests that mast cells may be more abundant in less aggressive tumor subtypes, but further investigation is needed to determine whether these cells contribute to tumor progression in these specific contexts or whether their presence simply reflects a more favorable tumor microenvironment.

Conclusion

Our study supports the multifaceted role of mast cells in breast cancer progression. The presence and density of mast cells in the tumor microenvironment may provide valuable insights into tumor behavior and patient prognosis. Understanding the complex interactions among mast cells, tumor cells, and the surrounding stroma could inform the development of novel therapeutic strategies aimed at modifying the immune landscape within tumors to improve clinical outcomes.

Future research should focus on clarifying the specific roles of mast cells across different breast cancer subtypes and exploring their potential as prognostic biomarkers and therapeutic targets.

Acknowledgements

None

Conflict of interest statement

None

Ethics Committee Approval: Muğla Sıtkı Koçman University Health Sciences Ethics Committee - 01.06.2021/210070-113

Funding: This study did not receive any funding support.

References

1. Raposo TP, Beirao BC, Pang L. et al. Inflammation and cancer: till death tears them apart. Vet J. 2015;205(2):161–74.
2. Galdiero MR, Garlanda C, Jaillon S, et al. Tumor associated macrophages and neutrophils in tumor progression. J Cell Physiol. 2013;228(7):1404–12.
3. Varricchi G, Galdiero MR, Loffredo S, et al. Are mast cells MASTers in cancer? Front Immunol. 2017;8:p. 424.
4. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. Curr Pharm Des. 2012;18(26):3831–52.
5. Baek JY, Li CY, Pardanani A, et al. Bone marrow angiogenesis in systemic mast cell disease. J Hematother Stem Cell Res. 2002 Feb;11(1):139-46.
6. Dvorak AM, Kissell S. Granule changes of human skin mast cells characteristic of piecemeal degranulation and associated with recovery during wound healing in situ. J Leukoc Biol. 1991;49(2):197–210.
7. Weidner N, Austen KF. Ultrastructural and immunohistochemical characterization of normal mast cells at multiple body sites. J Invest Dermatol. 1991;96: 26S-31S.
8. Theoharides CT, Conti, Mast cells: the JEKYLL and HYDE of tumor growth. Trends Immunol. 2004;25:235–41
9. Kashiwagi S, Yashiro M, Takashima T,et al. c-Kit expression as a prognostic molecular marker in patients with basal-like breast cancer. Br J Surg. 2013;100:490–6
10. Dabiri S, Huntsman D, Makretsov N, et al. The presence of stromal mast cells identifies a subset of invasive breast cancers with a favourable prognosis. Mod Pathol. 2004; 17:690–5
11. Ribatti D, Vacca A, Nico B, et al .The role of mast cells in tumour angiogenesis. Br J Haematol. 2001;115:514–21
12. Ch'ng S, Wallis RA, Yuan L, et al. Mast cells and cutaneous malignancies. Modern Pathology. 2005;19(1):149–59
13. Tuna B, Yorukoglu K, Unlu M, et al. Association of mast cells with microvessel density in renal cell carcinomas. Eur Urol. 2006;50(3):530–4.
14. Aponte-López A, Fuentes-Pananá EM, Cortes-Muñoz D, et al. Mast Cell, the Neglected Member of the Tumor Microenvironment: Role in Breast Cancer. J Immunol Res. 2018:2584243.
15. Eiro N, Vizoso FJ. Inflammation and cancer. World J Gastrointest Surg. 2012;4(3):62–72.
16. Fernandes JV, Cobucci RN, Jatoba CA, et al. The role of the mediators of inflammation in cancer development. Pathol Oncol Res. 2015;21(3):527–34.
17. Luo Y, Huang W, Zhang H,et al. Prognostic significance of CD117 expression and TP53 missense mutations in triple-negative breast cancer. Oncol Lett. 2018;15(5):6161-70.
18. Garbe JC, Pepin F, Pelissier FA, et al. Accumulation of multipotent progenitors with a basal differentiation bias during aging of human mammary epithelia. Cancer Res. 2012;72(14):3687-701.
19. WHO. World Health Organization. 2012. http://wwwwhoint/cancer/es/
20. Rajput AB, Turbin DA, Cheang MC, et al. Stromal mast cells in invasive breast cancer are a marker of favourable prognosis: a study of 4,444 cases. Breast Cancer Res Treat. 2008;107(2):249–57.
21. della Rovere F, Granata A, Familiari D, et al. Mast cells in invasive ductal breast cancer: different behavior in high and minimum hormone-receptive cancers. Anticancer Res. 2007;27(4B):2465–71.
22. West RB, Nuyten DS, Subramanian S, et al. Determination of stromal signatures in breast carcinoma. PLoS Biol. 2005;3:e187
23. Ranieri G, Ammendola M, Patruno R, et al. Tryptase-positive mast cells correlate with angiogenesis in early breast cancer patients. Int J Oncol. 2009;35(1):115–20.
24. Fakhrjou A, Naghavi-Behzad M, Montazeri V,et al. The relationship between histologic grades of invasive carcinoma of breast ducts and mast cell infiltration. South Asian J Cancer. 2016;5(1):5–7.
25. Keser SH, Kandemir NO, Ece D, et al. Relationship of mast cell density with lymphangiogenesis and prognostic parameters in breast carcinoma. Kaohsiung J Med Sci. 2017;33(4):171–80.
26. Löfdahl B, Ahlin C, Holmqvist M, et al. Inflammatory cells in node-negative breast cancer. Acta Oncol. 2012;51(5):680–6.
27. Norashikin AA, Shau KL, Roslina, Huzlinda H, Comparison of Mast Cell Density and Prognostic Factors in

InvasiveBreast Carcinoma: A Single-Centre Study in Malaysia. Malays J Med Sci. 2023;30(5):81–90.
28. Glajcar A, Szpor J, Pacek A, et al. The relationship between breast cancer molecular subtypes and mast cell populations in tumor microenvironment. Virchows Arch. 2017;470(5):505-15.
29. Xiang M, Gu Y, Zhao F, et al. Mast cell tryptase promotes breast cancer migration and invasion. Oncol Rep. 2010;23(3):615–9.
30. Samoszuk M, Kanakubo E, Chan JK. Degranulating mast cells in fibrotic regions of human tumors and evidence that mast cell heparin interferes with the growth of tumor cells through a mechanism involving fibroblasts. BMC Cancer. 2005;5(1):121.