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The relationship of changes in molecular subtypes with metastases and progression-free survival in breast cancer

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Abstract.
BACKGROUND: Molecular subtyping of breast cancer cells is increasingly being developed as an initial step in selecting therapy and predicting the prognosis of breast cancer patients. During breast cancer, the molecular subtype of cancer cells can change. This study aimed to analyze the relationship between changes in the intrinsic subtype of breast cancer with metastasis and progression-free survival in breast cancer patients.
METHODS: This was a retrospective cohort study of patients diagnosed with breast cancer from 2016 to 2021. The molecular subtypes from the immunohistochemical examination results were recorded twice, and metastasis and progression-free survival (PFS) were recorded. The data were analyzed using the chi-square test and SPSS 26.
RESULTS: Of the 44 patients, 19 (43.2%) experienced a change in molecular subtype, and 25 (56.8%) did not. No significant relationship existed between changes in molecular subtype and metastasis ($p = 0.405$). No significant relationship existed between changes in molecular subtype and PFS ($p = 0.900$). A significant relationship was found between changes in the molecular subtype and PFS in the patients with changes in the molecular subtype ($p = 0.022$).
CONCLUSIONS: Changes in the intrinsic subtype were associated with PFS in breast cancer patients. Patients with an intrinsic subtype that changed to triple-negative showed worse PFS.

Keywords: Breast cancer, metastasis, molecular subtype, progression-free survival

1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide. Approximately 2.3 million cases of breast cancer were diagnosed in 2020, with almost 50% of all cases and approximately 60% of deaths occurring in developing countries [1]. In the 2013 St Gallen Consensus, breast cancer subtypes were grouped into luminal A, luminal B, HER-2 positive, and triple-negative types. Luminal molecular subtypes are influenced by estrogen receptor (ER), progesterone receptor (PR), HeER-2, and Ki67 levels. Molecular subtyping helps determine the type

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of therapy to be given and describes each subtype's prognosis [2].

Progression-free survival (PFS) is the time elapsed between randomization and tumor progression or death from any cause, with the censoring of patients without events in the last series of lesion measurements verifying the lack of progression [3]. Breast cancer patients may experience changes in molecular subtypes during their disease. Little research has analyzed the relationship between the presence or absence of changes in the intrinsic subtype of breast cancer and metastasis and PFS.

2. Materials and methods

This was an observational analytical study with a retrospective cohort design. It was conducted on patients diagnosed with breast cancer from 2016 to 2021 at Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar. The inclusion criteria were women with breast cancer who were undergoing breast cancer treatment and had received immunohistochemical (IHC) examinations twice. The exclusion criteria were the absence of complete patient data from IHC examination results, other types of cancer (e.g., ovarian, liver, or lung cancer), and patients who could not be contacted for follow-up. The data collected were the presence or absence of changes in the intrinsic subtype of breast cancer based on the results of IHC examination, metastasis, and PFS.

2.1. Histopathological grading of breast cancer

Histopathological grading is divided into three groups based on an anatomical pathology examination: high, moderate, and low. This was determined from the nuclear pleomorphism, tubular formation, and mitotic index (based on the Scarff–Bloom–Richardson modification) [4].

2.2. Metastasis breast cancer

Metastases present when breast cancer was first diagnosed (de novo) were considered metastatic breast cancer. Breast cancer patients who presented for the first time with clinical symptoms and radiological signs of metastasis were investigated by chest X-ray, abdominal ultrasound, abdominal computerized tomography (CT) scan, thoraco-lumbosacral X-ray, vertebral magnetic resonance imaging (MRI), head CT scan, and brain MRI. The most common locations for breast cancer metastases are the bones, liver, lungs, and brain.

2.3. The molecular subtype of breast cancer

The molecular subtype classifications used were triple-negative, HER2, luminal B, and luminal A [5–7].

2.4. Progression-free survival (PFS)

PFS is the time between treatment and tumor progression or death from any cause as a surrogate endpoint for overall survival (OS). A surrogate endpoint is defined as a biomarker that is intended to replace a clinical endpoint. In this study, patients were followed up for 24 months, whether they experienced tumor progression or death from any cause.

3. Statistical analysis

The data analysis using SPSS version 26 (Armonk, NY, USA: IBM Corp). The statistical analyses included the chi-square test. A result was considered significant if the p-value was <0.05.

4. Results

A total of 44 samples were collected in this study: 19 patients (43.2%) experienced a change in molecular subtype during treatment, and 25 (56.8%) did not. Most patients were aged ≥45 years (68.2%), with histopathology grade 2 (56.8%) and tumor location on the left (47.7%). No significant differences existed in age, histopathology, grade, or tumor location between the group that experienced molecular subtype changes and whose molecular subtype remained fixed during treatment ($p > 0.05$; Table 1).

Most patients did not experience metastases (54.4%). Most with a changed molecular subtype experienced metastases (52.6%), whereas most with a fixed molecular subtype did not (60%). However, statistical tests showed no significant relationship between changes in molecular subtype and metastases ($p = 0.405$; Table 2).

A relationship between molecular subtype and metastases existed only in patients with a fixed molecular subtype; metastases occurred more frequently in patients with the triple-negative molecular subtype. Patients with the HER-2 molecular subtype were less likely to experience metastases. However, the statistical tests showed no significant relationship between

Table 1
Patient characteristics based on changes in molecular subtype

Characteristic	Molecular subtype change (n = 19)		Fixed molecular subtype (n = 25)		Total		p-value
	n	%	n	%	n	%	
Age (years)							
<45	4	21.1	10	40.0	14	31.8	0.181
≥45	15	78.9	15	60.0	30	68.2	
Histopathological grading							
1	3	15.8	4	16.0	7	15.9	
2	8	42.1	17	68.0	25	56.8	0.137
3	8	42.1	4	16.0	12	27.3	
Location							
Bilateral	2	10.5	1	4.0	3	6.8	
Right	9	47.4	11	44.0	20	45.5	0.630
Left	8	42.1	13	52.0	21	47.7	

Table 2
Association between changes in molecular subtype and breast cancer metastasis

Molecular subtype change	Metastases						p-value
	No (n = 20)		Yes (n = 24)		Total (n = 44)		
	n	%	n	%	N	%	
Changed	10	52.6	9	47.4	19	100	0.405
Fixed	10	40.0	15	60.0	25	100	

Note: Chi-square test.

Table 3
Association between molecular subtypes and breast cancer metastases in the fixed molecular subtype group

Molecular subtype	Metastases						p-value
	Yes (n = 20)		No (n = 24)		Total (n = 44)		
	n	%	n	%	N	%	
HER-2	3	30.0	7	46.7	10	40.0	0.410
Luminal A	0	0.0	1	6.7	1	4.0	
Luminal B	3	30.0	5	33.3	8	32.0	
Triple-negative	4	40.0	2	13.3	6	24.0	

Note: Chi-square test.

molecular subtypes and metastases in patients with a fixed molecular subtype (p = 0.410; Table 3).

A relationship between molecular subtype and metastases existed only in patients with a changed molecular subtype. Metastases occurred more in patients with a change from the luminal A to luminal B or HER-2 to luminal B molecular subtypes compared to patients with no change in the molecular subtype. Metastases occurred more frequently in patients who changed from the luminal B to triple-negative molecular subtypes. However, the statistical tests showed no significant relationship between molecular subtype changes and metastases in patients with a change in molecular subtype (p = 0.544; Table 4).

Most patients with changed or fixed molecular subtypes had a PFS of ≤12 months (56.8%). The statistical test results showed no significant relationship between changes in molecular subtype and PFS (p = 0.900; Table 5).

A relationship between molecular subtype and PFS existed only in patients whose molecular subtype remained fixed. A PFS of ≤12 months was more common in patients with the triple-negative molecular subtype, whereas a PFS of >12 months was more common in patients with the HER-2 and luminal B molecular subtypes. However, no significant relationship existed between the molecular subtype and PFS in the patients with fixed molecular subtype (p = 0.065; Table 6).

A relationship between molecular subtype and PFS existed only in patients with a change in molecular subtype. A PFS of ≤12 months occurred more frequently in patients who experienced a shift from luminal B to triple-negative molecular subtypes. A PFS of >12 months occurred more frequently in patients who experienced a change from the luminal B to luminal A molecular subtypes. A significant relationship existed

Table 4
Association between molecular subtypes and breast cancer metastases in the changed molecular subtype group

Molecular subtype	Metastases						*p*-value
	Yes (n = 20)		No (n = 24)		Total (N = 44)		
	n	%	*n*	%	N	%	
HER-2 to luminal B	2	20.0	1	11.1	3	15.8	0.544
Luminal A to HER-2	0	0.0	1	11.1	1	5.3	
Luminal A to luminal B	2	20.0	1	11.1	3	15.8	
Luminal A to triple-negative	1	10.0	0	0.0	1	5.3	
Luminal B to HER-2	2	20.0	0	0.0	2	10.5	
Luminal B to luminal A	1	10.0	2	22.2	3	15.8	
Luminal B to triple-negative	1	10.0	3	33.3	4	21.1	
Triple-negative to luminal B	1	10.0	1	11.1	2	10.5	

Note: Chi-square test.

Table 5
Association between changes in molecular subtype and breast cancer PFS

Molecular subtype change	PFS (months)						*p*-value
	≤12 (n = 25)		>12 (n = 19)		Total (N = 44)		
	n	%	*n*	%	*n*	%	
Changed	11	57.9	8	42.1	19	100	0.900
Fixed	14	56.0	11	44.0	25	100	

Note: Chi-square test.

Table 6
Association between molecular subtype and breast cancer PFS in the fixed molecular subtype group

Molecular subtype	PFS (months)						*p*-value
	≤12 (n = 25)		>12 (n = 19)		Total (N = 44)		
	N	%	N	%	*n*	%	
HER-2	5	35.7	5	45.5	10	40.0	0.065
Luminal A	0	0.0	1	9.1	1	4.0	
Luminal B	3	21.4	5	45.5	8	32.0	
Triple-negative	6	42.9	0	0.0	6	24.0	

Note: Chi-square test.

between the shift in the molecular subtype and the PFS in patients with a changed molecular subtype (p = 0.022; Table 7).

5. Discussion

Most breast cancer patients did not experience metastases (54.4%). Most patients with a changed molecular subtype experienced metastases (52.6%), whereas most with a fixed molecular subtype did not (60%). However, no significant relationship existed between changes in molecular subtype and metastasis. Therefore, changes in molecular subtypes were not associated with breast cancer metastasis. The results also showed that the molecular subtype and changes in the molecular subtype were not related to the incidence of metastases.

The patients with a changed molecular subtype included changes from HER-2 and triple-negative to luminal B and from luminal A and luminal B to other molecular subtypes. Turner et al. [8] reported that emerging evidence suggests that intratumoral molecular subtypes are not static; instead, plasticity between different subtypes may occur. Interconversion between different subtypes within a tumor drives tumor progression, metastasis, and treatment resistance. Evidence shows a transition from primary HER-2 to HER-2 brain metastases due to the microenvironment in the brain providing a place that supports HER-2 signaling. Dynamic conversion between subtypes does not only occur in brain metastases. Conversion depends on the metastatic tumor environment, with ER conversion rates higher in the bone and central nervous system and lower in the liver. However, the exact mechanism for these expression changes remains to be elucidated. Three potential explanations are the area selection for preexisting clones that may be masked by signs of large tumors that may mask changes in ER, PR, and HER-2 molecular expression and a combination of both. Luminal to HER-2 and triple-negative to HER-2 conversion can give rise to metastases due to

Table 7
Association between molecular subtype and breast cancer PFS in the changed molecular subtype group

Molecular subtype	PFS (months)						*p*-value
	≤12 (*n* = 25)		>12 (*n* = 19)		Total (*N* = 44)		
	n	%	*n*	%	*n*	%	
HER-2 to luminal B	0	0.0	3	37.5	3	15.8	0.022
Luminal A to HER-2	1	9.1	0	0.0	1	5.3	
Luminal A to luminal B	2	18.2	1	12.5	3	15.8	
Luminal A to triple-negative	1	9.1	0	0.0	1	5.3	
Luminal B to HER-2	2	18.2	0	0.0	2	10.5	
Luminal B to luminal A	0	0.0	3	37.5	3	15.8	
Luminal B to triple-negative	4	36.4	0	0.0	4	21.1	
Triple-negative to luminal B	1	9.1	1	12.5	2	10.5	

Note: Chi-square test.

the discordance in molecular signatures due to temporal evolution and a favorable metastatic niche [8]. Another study stated that one in four triple-negative primary tumors is converted to another subtype in the liver, which explains the presence of liver metastases [9].

In this study, the molecular subtypes that experienced changes were mostly luminal B, followed by luminal A. These results are similar to previous studies in that changes in gene expression and subsequent subtype conversion occurred on a larger scale in metastatic luminal type A breast cancer compared to other molecular subtypes. This underscores the importance of molecular changes in metastatic disease, especially in tumors that initially have low aggressive potential. Subtype conversion only partially reflects changes that occur in tumor evolution. Without changes in the luminal A subtype, the molecular phenotype may still differ in metastases, especially in low-grade tumors. When luminal A subtype conversion occurs, it can be considered an indicator of genetic remodeling in metastases and a risk factor for developing additional disease. This was also evident in the change in the recurrence risk score, which was almost doubled in luminal A-type cancer. The status of ER and HER2 as predictive clinical markers remained unchanged, the proliferation rate increased significantly, and breast hormone receptor signaling decreased. Gene expression changes seen in all subtypes included evidence of increased mobility and invasive behavior of metastatic tumor cells through downregulation of cytokeratins (*KRT5/14*), tumor activation through downregulation of *MMP1130/31*, and de-activation of ER-dependent pathways, as demonstrated by downregulation of the PR and ankyrin repeat domain gene (*ANKRD30A*). In contrast, genes involved in epithelial-mesenchymal transition and growth signaling are upregulated across all molecular subtypes [10].

In this study, the majority of patients with fixed molecular subtypes had the HER-2 molecular subtype, followed by luminal B2, triple-negative, and luminal A. Tedjamartono et al. reported that HER-2 expression in brain metastases occurred in 55% of cases. HER-2 overexpression is significantly associated with brain metastases [11]. Breast cancer patients with HER-2 overexpression are 4,889 times more at risk of developing brain metastases compared to HER-2-negative patients. Tumors with HER-2 overexpression have a significantly higher risk of distant metastasis compared with HER-2-negative tumors and show a higher potential for central nervous system and lung metastases and a low risk of recurrence and the development of bone disease [12].

Another study reported that patients with HER-2−/HoR+ status had more bone metastases, whereas patients with HER-2+/HoR− status had an increased incidence of liver metastases. Brain and lung metastases are more likely in women with HER-2−/HoR− status [13]. The triple-negative and HER-2+ subtypes metastasize to vital organs such as the brain and lungs more often than the luminal A subtype, thus potentially causing earlier death [14]. The triple-negative subtype increases the risk of visceral and brain metastases. Molecular subtypes can predict the preferred location of distant metastases, emphasizing that this association is helpful in surveillance options and developing appropriate cancer screening and management strategies for follow-up and therapy [15].

Wang et al. found no statistical difference in lymphatic metastasis between various breast cancer molecular subtypes [16]. However, the rate of distant metastasis in patients with HER-2 type breast cancer was significantly higher than in patients with the other three subtypes. Differences in local metastases between molecular subtypes were not significant. Abiltayeva et al. reported no significant relationship between molecular subtype and metastasis location [17].

In this study, metastases occurred more in the group that did not experience a change in molecular subtype compared to the group that did, but this was not significant. This is because each molecular subtype tends to metastasize in different organs. This study only studied the relationship between molecular subtypes based on the general incidence of metastases.

No significant relationship existed between PFS and changes in the molecular subtype. The results also showed no significant association between molecular subtype and PFS in patients with a fixed molecular subtype. However, a significant association was found between changes in molecular subtypes and PFS in patients with changed molecular subtypes. The results of this study align with research by Stefanovic et al., who reported no relationship between PFS and stability of the intrinsic subtype. PFS did not differ between luminal and triple-negative patients in the subpopulations of altered molecular subtypes and persistent molecular subtypes [18].

In this study, patients with changed and fixed molecular subtypes mostly had a PFS of ≤12 months. This shows that breast cancer patients mostly show a poor prognosis. Previous studies have reported that the most significant proportion of PFS events in metastatic cancer occurred within 12 months [19].

A PFS of ≤12 months was often found in triple-negative patients; those with a survival time free from tumor development or progression of less than 12 months mostly had the triple-negative molecular subtype. However, no difference existed in PFS based on molecular subtype. Similar to this study, Bonotto et al. reported that the highest PFS occurred in luminal A and the lowest in triple-negative breast cancer. PFS was proposed as a potential replacement for OS that allows faster evaluation of new drugs [20]. In this study, HER-2 was more commonly found with a PFS of >12 months. Serrano et al. found that PFS was worse in breast cancer with a HER-2 score of 2+ compared to 1+ [21]. Rugo et al. reported that trastuzumab deruxtecan significantly improved PFS in patients with HR+ and HER-2 low metastatic breast cancer. Most patients had visceral metastases (95%), consistent with aggressive disease, and had received multiple lines of chemotherapy, which are factors associated with shorter PFS and a higher risk of neutropenia [22].

In this study, most patients with the luminal B subtype had a PFS of >12 months; patients with a survival time free from tumor development or progression of more than 12 months mostly had the luminal B molecular subtype. These results align with previous studies finding that luminal B does not show tumor progression and has better PFS than non-luminal subtypes. The median PFS rates in the luminal B and non-luminal groups were 20.0 months and 13.11 months, respectively, and the difference was statistically significant [16]. A similar study reported a statistically substantial PFS difference between luminal and non-luminal disease (median PFS 10.5 months vs. 3.5 months) [23]. The non-luminal subtype was independently associated with worse PFS and OS other subtypes. Similar to the results of different trials, the difference in median PFS between the two groups was statistically significant: 6.67 months in the luminal group versus 5.16 months in the non-luminal group, with an adjusted hazard ratio of 0.66 [24]. The PFS of patients with HER-2− luminal B breast cancer was better than that of patients with HER-2+ luminal B breast cancer. Cross-talk between HER-2 and ER, signaling pathways in breast cancer, contributes to resistance to hormonal therapy. The combination of trastuzumab and anastrozole resulted in a statistically significant improvement in PFS in women with luminal B HER-2+ breast cancer [17]. However, this study found no differences in PFS based on molecular subtypes because it did not differentiate between luminal and non-luminal.

A significant difference in PFS existed based on the type of molecular subtype change. Patients who experienced a shift in molecular subtype had a PFS of ≤12 months, which occurred more often in patients who changed from the luminal B to triple-negative molecular subtypes. A PFS of >12 months occurred more often in patients who experienced a change from the luminal B to luminal A molecular subtypes. This means that patients changing from luminal B to triple-negative subtypes have a shorter survival time free from tumor development or progression compared to those with other changes in molecular subtypes. Similar results have been reported in previous studies. Changes in common subtypes (to triple-negative or luminal subtypes) reflect a general tendency towards mutations so that the cancer becomes more aggressive [18].

Grigoryeva et al. [25] observed changes in molecular subtypes in 90% of untreated breast cancer patients and 82% of those treated with neoadjuvant chemotherapy. Changes in molecular subtypes were more diverse in patients treated with neoadjuvant chemotherapy. Molecular subtype changes more frequently result in unfavorable variants in circulating tumor cells. Patients with inadequate therapy were characterized by decreased simulated 5-year metastasis-free survival compared with patients receiving appropriate therapy treatment. Thus, detecting molecular subtype changes in circulating tumor cells may be a tool for optimizing antitumor therapy. Changes in the molecular interface of cancer cells during tumor growth and progression can be associated with many adverse effects, such as drug resistance, local recurrence, and metastatic spread. HR/HER-2 status and Ki-67 expression in tumor cells determine molecular subtype classification and treatment decisions in breast cancer patients [25].

The results of this study indicate that fixed and changing molecular subtypes are associated with similar disease progression. Differences in disease progression occur due to differences in molecular subtype changes. Changing to the triple-negative molecular subtype resulted in worse tumor development outcomes compared to other subtypes.

A limitation of this study is that it grouped the incidence of metastases in general and did not classify them based on location. Additionally, the data were limited because not all combinations of molecular subtype changes were present in the study samples.

6. Conclusion

In summary, intrinsic subtype changes were not associated with metastasis in breast cancer patients. Changes in inherent subtype were associated with PFS: the intrinsic subtype that changed to triple-negative had worse PFS. These results imply that examining changes in intrinsic subtypes may be helpful in guiding the effectiveness of treatment in breast cancer patients. Further research is needed with more data to obtain all groups of molecular subtype changes related to the location of metastases and PFS.

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Ethics approval

The study was approved by the Research Ethics Committee of the Faculty of Medicine Universitas Hasanuddin, Makassar, Indonesia, number 859/UN4.6.4.5.31/PP36/2023. We promised that the participants' data would be anonymized or maintained with confidentiality, that the rights or interests of participants would not be invaded, and that informed consent would be obtained from all individual participants.

Competing interests

No competing interests were reported.

Data availability statement

Data is accessible upon justifiable request.

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References

[1] Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K et al., Global patterns of breast cancer incidence and mortality: A population based cancer registry data analysis from 2000 to 2020, *Cancer Communications*, 8 16. 41(11): 1183–1194, 2021. doi:10.1002/cac2.12207.

[2] Badar F, Faruqui ZS, Uddin N, Trevan EA, Management of breast lesions by breast physicians in a heavily populated South Asian developing country, *Asian Pacific J Cancer Prev*, 12: 827–832, 2011.

[3] Hotte SJ, Bjarnason GA, Heng DYC, Jewett MAS, Kapoor A, Kollmannsberger C et al., Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma, *Curr Oncol*, 18: 11–19, 2011. doi:10.3747/co.v18i0.941.

[4] van Dooijeweert C, van Diest PJ, Ellis IO, Grading of invasive breast carcinoma: The way forward, *Virchows Arch*, 480: 33–43, 2022. doi:10.1007/s00428-021-03141-2.

[5] Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J et al., Breast cancer intrinsic subtype classification, clinical use and future trends, *Am J Cancer Res*, 5: 2929–2943, 2015. http://www.ncbi.nlm.nih.gov/pubmed/26693050.

[6] Kumar V, Abbas A, Aster J, Female genital system and breast, in: Kumar V, Abbas A, Aster J (eds), Robbins Basic Pathol. 10th ed., Elsevier, 2017, https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=5553745.

[7] Pranoto AS, Haryasena H, Prihantono P, Rahman S, Sampepajung D, Indra I et al., The expression of programmed death-ligand 1 and its association with histopathological grade, stage of disease, and occurrence of metastasis in breast cancer, *Breast Dis*, 40: S71–S76, 2021. doi:10.3233/BD-219010.

[8] Turner KM, Yeo SK, Holm TM, Shaughnessy E, Guan JL, Heterogeneity within molecular subtypes of breast cancer, *Am J Physiol - Cell Physiol*, 321: C343–C354, 2021. doi:10.1152/ajpcell.00109.2021.

[9] Sundén M, Norgren S, Lundqvist R, Andersson A, Sund M, Hemmingsson O, Receptor conversion and survival in breast cancer liver metastases, *Breast Cancer Res*, 25: 105, 2023. doi:10.1186/s13058-023-01706-4.

[10] Klebe M, Fremd C, Kriegsmann M, Kriegsmann K, Albrecht T, Thewes V et al., Frequent molecular subtype switching and gene expression alterations in lung and pleural metastasis from luminal A–type breast cancer, *JCO Precis Oncol*, 4: 848–859, 2020. doi:10.1200/po.19.00337 .

[11] Tedjamartono TD, Sudarsa IW, Winata A, Manik NGAA, Wetan Y, Overekspresi HER-2 sebagai faktor risiko terjadinya metastasis otak pada pasien kanker payudara, *J Med Udayana*, 9: 58–64, 2020.

[12] Courtinard C, Gourgou S, Jacot W, Carton M, Guérin O, Vacher L et al., Association between progression-free survival and overall survival in women receiving first-line treatment for metastatic breast cancer: Evidence from the ESME real-world database, *BMC Med*, 21: 1–13, 2023. doi:10.1186/s12916-023-02754-5.

[13] Gong Y, Liu Y-R, Ji P, Hu X, Shao Z.-M., Impact of molecular subtypes on metastatic breast cancer patients: A SEER population-based study, *Sci Rep*, 7: 45411, 2017. doi:10.1038/srep45411.

[14] Wijayanto A, Pieter JSLA, Prihantono P, Syamsu SA, Thaufix NS, Abdi A, Survivability rates based on molecular subtype, stage and metastasis of 36 months cohort in breast cancer patients, *Nusant Med Sci J*, 7: 29–38, 2022. doi:10.20956/nmsj.v7i1.20092.

[15] Fan JH, Zhang S, Yang H, Yi ZB, Ouyang QC, Yan M et al., Molecular subtypes predict the preferential site of distant metastasis in advanced breast cancer: A nationwide retrospective study, *Front Oncol*, 13: 1–12, 2023. doi:10.3389/fonc.2023.978985.

[16] Wang GS, Zhu H, Bi SJ, Pathological features and prognosis of different molecular subtypes of breast cancer, *Mol Med Rep*, 6: 779–782, 2012. doi:10.3892/mmr.2012.981.

[17] Abiltayeva A, Moore MA, Myssayev A, Adylkhanov T, Baissalbayeva A, Zhabagin K et al., Clinical, histopathological and molecular characteristics of metastatic breast cancer in north-eastern Kazakhstan: A 10 year retrospective study, *Asian Pacific J Cancer Prev*, 17: 4797–4802, 2016. doi:10.22034/APJCP.2016.17.10.4797.

[18] Stefanovic S, Deutsch TM, Wirtz R, Hartkopf A, Sinn P, Kohler M et al., Impact of mRNA-assessed molecular subtype conversion, intact and apoptotic circulating tumor cells on survival of metastatic breast cancer patients: Proof of principle, *Diagnostics*, 10: 369, 2020. doi:10.3390/diagnostics10060369 .

[19] Pietrantonio F, Lonardi S, Corti F, Infante G, Elez ME, Fakih M et al., Nomogram to predict the outcomes of patients with microsatellite instability-high metastatic colorectal cancer receiving immune checkpoint inhibitors, *J Immunother Cancer*, 9: 1–9, 2021. doi:10.1136/jitc-2021-003370.

[20] Bonotto M, Gerratana L, Poletto E, Driol P, Giangreco M, Russo S et al., Measures of outcome in metastatic breast cancer: Insights from a real-world scenario, *Oncologist*, 19: 608–15, 2014. doi:10.1634/theoncologist.2014-0002.

[21] Saavedra Serrano C, Pérez Mies B, Gion Cortes M, Cortes Salgado A, Fernández Abad M, Martinez-Jañez N et al., 121P Impact of HER2 low (H2L) expression on prognosis in luminal locally advanced or metastatic breast cancer (BC): A retrospective study, *Ann Oncol*, 32: S73, 2021. doi:10.1016/j.annonc.2021.03.135.

[22] Rugo HS, Bardia A, Marmé F, Cortés J, Schmid P, Loirat D et al., Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): A randomised, open-label, multicentre, phase 3 trial, *Lancet*, 402: 1423–1433, 2023. doi:10.1016/S0140-6736(23)01245-X.

[23] Kim J, Lee Y, Yoo T, Kim J, Hyun J, Park I et al., Organ-specific recurrence or metastatic pattern of breast cancer according to biological subtypes and clinical characteristics, *J Breast Dis*, 7: 30–37, 2019. doi:10.14449/jbd.2019.7.1.30.

[24] Park S, Koo JS, Kim MS, Park HS, Lee JS, Lee JS et al., Characteristics and outcomes according to molecular subtypes of breast cancer as classified by a panel of four biomarkers using immunohistochemistry, *Breast*, 21: 50–57, 2012. doi:10.1016/j.breast.2011.07.008.

[25] Grigoryeva ES, Tashireva LA, Alifanov VV, Savelieva OE, Vtorushin SV, Zavyalova MV et al., Molecular subtype conversion in CTCs as indicator of treatment adequacy associated with metastasis-free survival in breast cancer, *Sci Rep*, 12: 20949, 2022. doi:10.1038/s41598-022-25609-0.