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Evaluation of the concordance of ER, PR, HER2, and Ki-67 expression levels between primary breast tumors and their liver metastases: a retrospective analysis of 57 cases

Primer meme tümörleri ile karaciğer metastazları arasında ER, PR, HER2 ve Ki-67 ekspresyon uyumunun değerlendirilmesi: 57 olgunun retrospektif analizi

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Abstract

Purpose: This study aims to evaluate the changes in estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 expression between primary breast tumors and their liver metastases.

Materials and methods: A total of 57 patients with breast cancer liver metastases were included. Immunohistochemical staining was performed to assess ER, PR, HER2, and Ki-67 expression in both primary and metastatic tumors. HER2 status was confirmed by silver in situ hybridization (SISH) when necessary. Statistical analyses were conducted to evaluate changes in biomarker expression.

Results: Comparison of biomarker expression between primary and metastatic biopsies revealed changes in ER status in 5 cases (1 from negative to positive, 4 from positive to negative); PR status in 22 cases (4 from negative to positive, 18 from positive to negative); HER2 status in 5 cases (2 from negative to positive, 3 from positive to negative); and Ki-67 status in 13 cases (6 from low to high, 7 from high to low). The discordance rates for ER, PR, HER2, and Ki-67 were calculated as 8.8%, 38.6%, 8.8%, and 28.9%, respectively.

Conclusion: Our findings confirm that biomarker expression may change between primary and metastatic breast cancer lesions. Given the crucial role of receptor status in treatment decisions, re-biopsy of metastatic lesions is essential to guide personalized therapy.

Keywords: Breast cancer, estrogen receptor, progesterone receptor, HER2, discordance.

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Öz

Amaç: Bu çalışma, primer meme tümörleri ile karaciğer metastazları arasındaki östrojen reseptörü (ER), progesteron reseptörü (PR), insan epidermal büyüme faktörü reseptörü 2 (HER2) ve Ki-67 ekspresyonundaki değişiklikleri değerlendirmeyi amaçlamaktadır.

Gereç ve yöntem: Meme kanseri karaciğer metastazı bulunan toplam 57 hasta çalışmaya dahil edilmiştir. Primer ve metastatik tümörlerde ER, PR, HER2 ve Ki-67 ekspresyonunu değerlendirmek için immünohistokimyasal boyama uygulanmıştır. Gerekli durumlarda HER2 durumu, silver in situ hibridizasyon (SISH) yöntemi ile doğrulanmıştır. Biyomarker ekspresyonundaki değişiklikleri değerlendirmek amacıyla istatistiksel analizler yapılmıştır.

Bulgular: Primer ve metastatik biyopsiler arasındaki biyobelirteç ekspresyonları karşılaştırıldığında, 5 olguda ER durumunda değişiklik (1 olgu negatiften pozitife, 4 olgu pozitiften negatife), 22 olguda PR durumunda değişiklik (4 olgu negatiften pozitife, 18 olgu pozitiften negatife), 5 olguda HER2 durumunda değişiklik (2 olgu negatiften pozitife, 3 olgu pozitiften negatife) ve 13 olguda Ki-67 durumunda değişiklik (6 olgu düşükten yükseğe, 7 olgu yüksekten düşüğe) saptanmıştır. ER, PR, HER2 ve Ki-67 için diskordans oranları sırasıyla %8,8, %38,6, %8,8 ve %28,9 olarak hesaplanmıştır.

Sonuç: Bulgularımız, primer ve metastatik meme kanseri lezyonları arasında biyobelirteç ekspresyonunda değişiklikler olabileceğini doğrulamaktadır. Reseptör durumunun tedavi kararlarındaki kritik rolü göz önünde bulundurulduğunda, metastatik lezyonlardan yeni biyopsi yapılması, kişiye özel tedavi planlamasında önemli bir yol gösterici olabilir.

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Anahtar kelimeler: Meme kanseri, östrojen reseptörü, progesteron reseptörü, HER2, diskordans.

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Introduction

The most frequently diagnosed cancer in women is breast cancer [1]. Even though breast cancer generally has a better prognosis compared to other malignant tumors, it is still the second highest cause of cancer-related mortality in women worldwide [2]. Approximately 20% of early-stage breast cancers eventually develop metastatic disease, and about 5% of newly diagnosed cases present as stage IV [1]. Notably, recurrence in the form of local relapse or distant metastasis can occur even after complete treatment and remission, sometimes up to ten years later [3]. In metastatic breast cancer, the choice of systemic treatment depends primarily on the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), with Ki-67 serving as an additional prognostic marker [4]. Historically, treatment decisions were based on the biomarker status of the primary tumor, since biopsies of metastatic lesions and reassessments of receptor status were not routinely performed. Yet, accumulating evidence now reveals notable discrepancies between hormone receptor profiles in primary breast tumors and their distant metastases [5-8]. Therefore, receptor status alterations can significantly impact treatment decisions and clinical outcomes, prompting recent international guidelines to advocate for the re-biopsy of accessible metastatic lesions [9-11]. This study focuses on liver biopsies, as the liver is a common metastatic site, and biopsy procedures are relatively straightforward and less prone to artifacts compared to bone biopsies, which can be affected by acid decalcification processes. Here, we investigate the discordance in ER, PR, HER2, and the prognostically significant Ki-67 expression between primary breast tumors and their liver metastases.

Material and methods

Study cohort and biomarker evaluation

Between 2015 and 2024, patients diagnosed with breast carcinoma liver metastasis via liver biopsy at our hospital were evaluated. Cases were included in the study if they had undergone a breast biopsy, breast excision, or mastectomy with documented ER, PR, and HER2 status. A total of 57 cases meeting these criteria were identified. For biomarker assessment in both primary and metastatic tissues, staining percentages for ER, PR, and Ki-67 were recorded within a range of 0% to 100%. ER and PR were considered positive if the staining percentage was ≥1% and negative if <1%. Ki-67 expression was categorized as low proliferation if the proliferation index was ≤14% and high proliferation if it was >14%. HER2 immunohistochemical (IHC) staining was evaluated based on staining intensity, classified as 0, 1+, 2+, or 3+. For cases with a HER2 score of 2+ (equivocal), silver in situ hybridization (SISH) was performed to determine the definitive HER2 status. Cases with HER2 scores of 0, 1+, or 2+ (SISH-negative) were classified as HER2-negative, whereas cases with scores of 2+ (SISH-positive) and 3+ were classified as HER2-positive.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of data distribution. Fisher's exact test (or Pearson's chi-square test), the Wilcoxon test, the kappa test, and the Friedman test were applied to analyze concordance and discordance in biomarker expression. Statistical analyses were conducted using IBM® SPSS® (version 25.0), with results considered statistically significant at $p<0.05$.

This study was approved by the Manisa Celal Bayar University Health Sciences Ethics Committee (approved date: 12.02.2025, approved number: 20478486-2877).

Results

All of the cases in this study were female. The ages of the patients ranged from 35 to 83, with a median age of 54 and a mean age of 54.44. Tumor types included invasive ductal carcinoma (IDC) in 50 cases (87.7%), invasive lobular carcinoma (ILC) in 3 cases (5.3%), IDC+ILC in 1 case (1.8%), carcinoma with apocrine differentiation in 1 case (1.8%), invasive papillary carcinoma in 1 case (1.8%), and metaplastic carcinoma in 1 case (1.8%).

In primary breast tumors, ER expression ranged from 0% to 90%, with a median of 70% and a mean of 55.07%. According to these values, 49 cases (86.0%) were found to be ER-positive (≥1%), and 8 cases (14.0%) were ER-negative (<1%). PR ranged from 0% to 95%, with a median value of 5% and a mean value of 21.05%. Based on these values, 32 cases (56.1%) were PR-positive (≥1%), and 25 cases (43.9%) were PR-negative (<1%). Of the cases, 26 (45.6%) were evaluated as HER2 IHC 0, 16 (28.1%) as 1+, 7 (12.3%) as 2+, and 8 (14.0%) as 3+. SISH was performed on the cases with HER2 IHC 2+ to determine the definitive HER2 status. Based on these results, 46 cases (80.7%) were HER2-negative (IHC 0, 1+, 2+ and SISH negative), and 11 cases (19.3%) were HER2-positive (IHC 3+, IHC 2+ and SISH positive). Ki-67 IHC staining was performed on 50 cases. In these cases, the Ki-67 proliferation index ranged from 5% to 70%, with a median value of 27.5% and a mean value of 34.2%. According to these values, 8 cases (16%) were classified into the Ki-67-low group (≤14%), and 42 cases (84%) were classified into the Ki-67-high group (>14%).

In the liver metastasis biopsies performed following diagnosis, ER, PR, and HER2 were also assessed. In the metastatic tissues, ER ranged from 0% to 100%, with a median value of 70% and a mean value of 58.096%. Based on these values, 46 cases (80.7%) were found to be ER-positive (≥1%), and 11 cases (19.3%) were ER-negative (<1%). PR ranged from 0% to 90%, with a median value of 0% and a mean value of 10.421%. According to these values, 18 cases (31.6%) were PR-positive (≥1%), and 39 cases (68.4%) were PR-negative (<1%). Of the cases, 33 (57.9%) were evaluated as HER2 IHC 0, 10 (17.5%) as 1+, 5 (8.8%) as 2+, and 9 (15.8%) as 3+. SISH was performed on the cases with HER2 IHC 2+ to determine the definitive HER2 status. Based on these results, 47 cases (82.5%) were HER2-negative (IHC 0, 1+, 2+ and SISH negative), and 10 cases (17.5%) were HER2-positive (IHC 3+, IHC 2+ and SISH positive). Ki-67 IHC staining was performed on 47 cases. In these cases, the Ki-67 proliferation index ranged from 1% to 95%, with a median value of 40% and a mean value of 41.55%. According to these values, 8 cases (17%) were classified into the Ki-67-low group (≤14%), and 39 cases (83%) were classified into the Ki-67-high group (>14%).

A comparative analysis of ER status between primary and metastatic biopsies revealed an increase in 24 cases (42.1%), a decrease in 16 cases (28.1%), and no change in 17 cases (29.8%) (Figure 1). However, this change was not statistically significant (Wilcoxon test; Z=-0.990, p=0.322). Overall, ER levels in metastatic tissues tended to be slightly higher, but this difference was also not statistically significant (Friedman test; χ^2=1.600, p=0.206). These findings indicate that while individual variations are present, there is no statistically significant change in ER status between primary and metastatic tissues. When ER status was analyzed categorically as ER-positive and ER-negative, 1 case (1.8%) changed from ER-negative to ER-positive, while 4 cases (7.0%) changed from ER-positive to ER-negative. The discordance rate was calculated as 8.8% (Table 1). The kappa test for concordance analysis yielded a value of 0.686, indicating a good level of concordance, with a low probability of this concordance occurring by chance (p=0.0001). Finally, Fisher's exact test was conducted to assess the statistical significance of ER changes, revealing a significant difference (p=0.0001). This finding suggests that the change in ER status between the two biopsies is not randomly distributed and represents a meaningful difference.

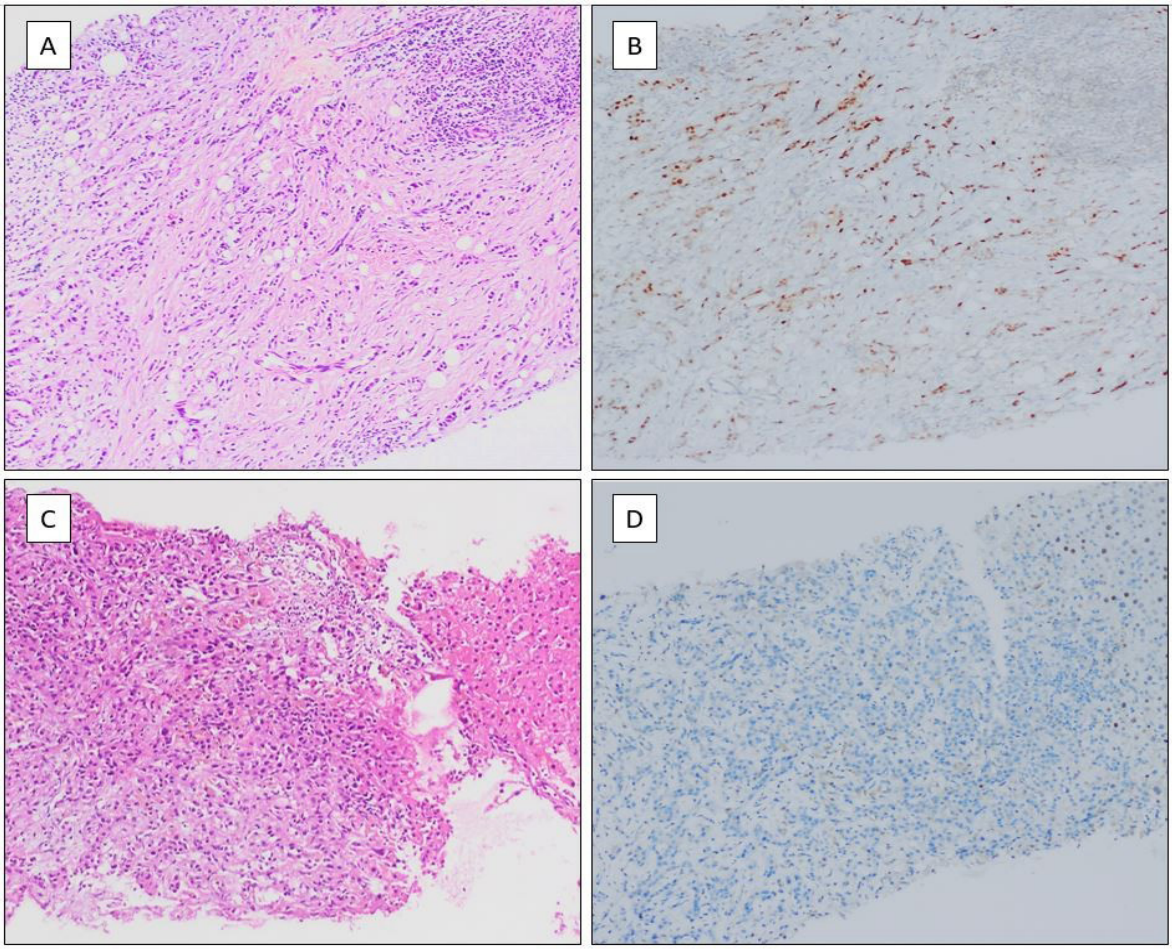

Figure 1. Breast biopsy of case number 56 (A; H&E, x100) and 70% ER positivity in the primary tumor (B; x100); liver biopsy of the same case (C; H&E, x100) and ER negativity in the metastatic tumor (D; x100)

Evaluation of the PR status between the two biopsies revealed an increase in PR levels in 11 cases (19.3%), a decrease in 26 cases (45.6%), and no change in 20 cases (35.1%) (Figure 2, and Figure 3). The statistical analysis revealed that this change was significant (Wilcoxon test; Z=-2.891, p=0.004). Therefore, there is a notable difference in PR levels between the primary and metastatic tissues. The PR values in the primary tumor were higher compared to those in the metastatic tissue, and this difference was statistically significant (Friedman test; χ^2=6.081, p=0.014). These results suggest that a significant decrease in PR levels may occur during metastasis. When the PR values were analyzed by categorizing them as PR-positive and PR-negative, 4 cases (7.0%) changed from PR-negative to PR-positive, while 18 cases (31.6%) changed from PR-positive to PR-negative. The discordance rate for PR was calculated as 38.6% (Table 1). The kappa test applied showed weak concordance between the PR values (kappa=0.261, p=0.025). This indicates that the PR levels exhibited variability, and there was no strong consistency between the two biopsies. Finally, Fisher's exact test was applied to determine whether the change in PR values was statistically significant, and the results showed a significant difference (p=0.043). This suggests that the change in PR status between the two biopsies is not randomly distributed and represents a meaningful difference.

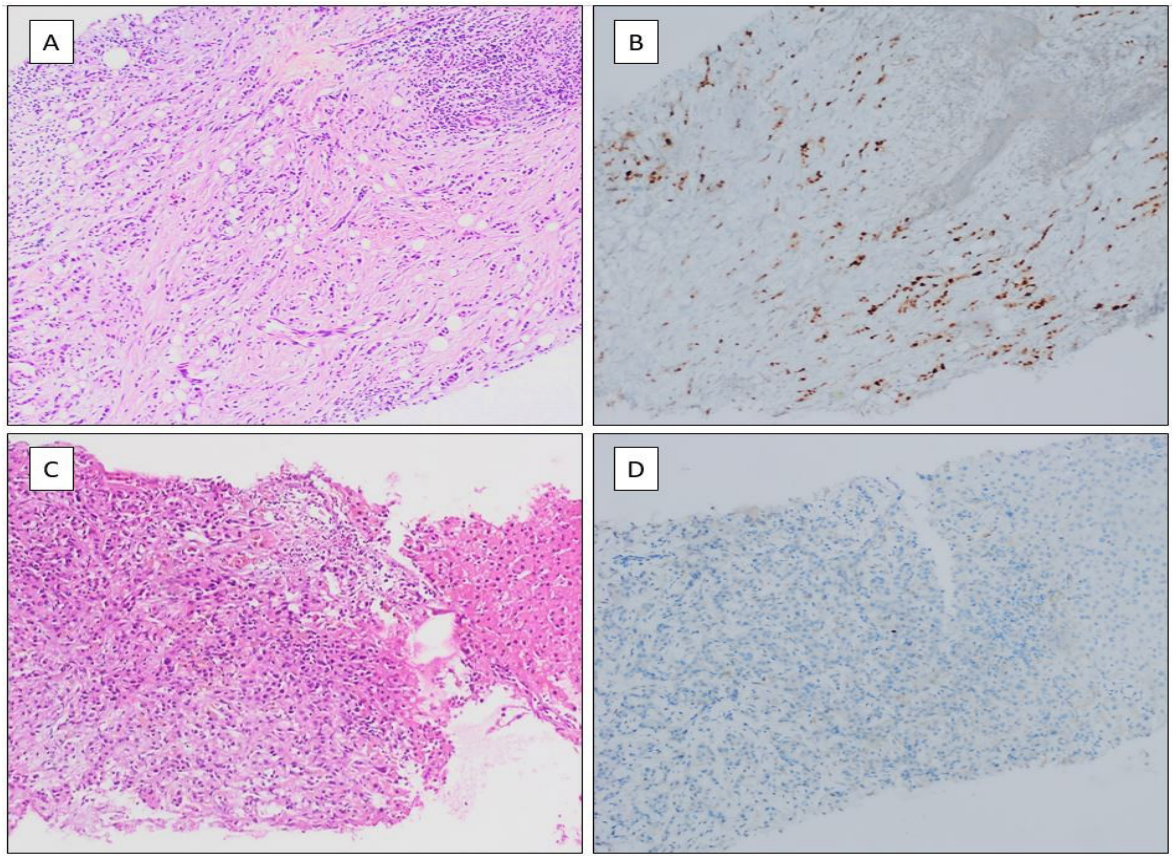

Figure 2. Breast biopsy of case number 56 (A; H&E, x100) and 60% PR positivity in the primary tumor (B; x100); liver biopsy of the same case (C; H&E, x100) and PR negativity in the metastatic tumor (D; x100)

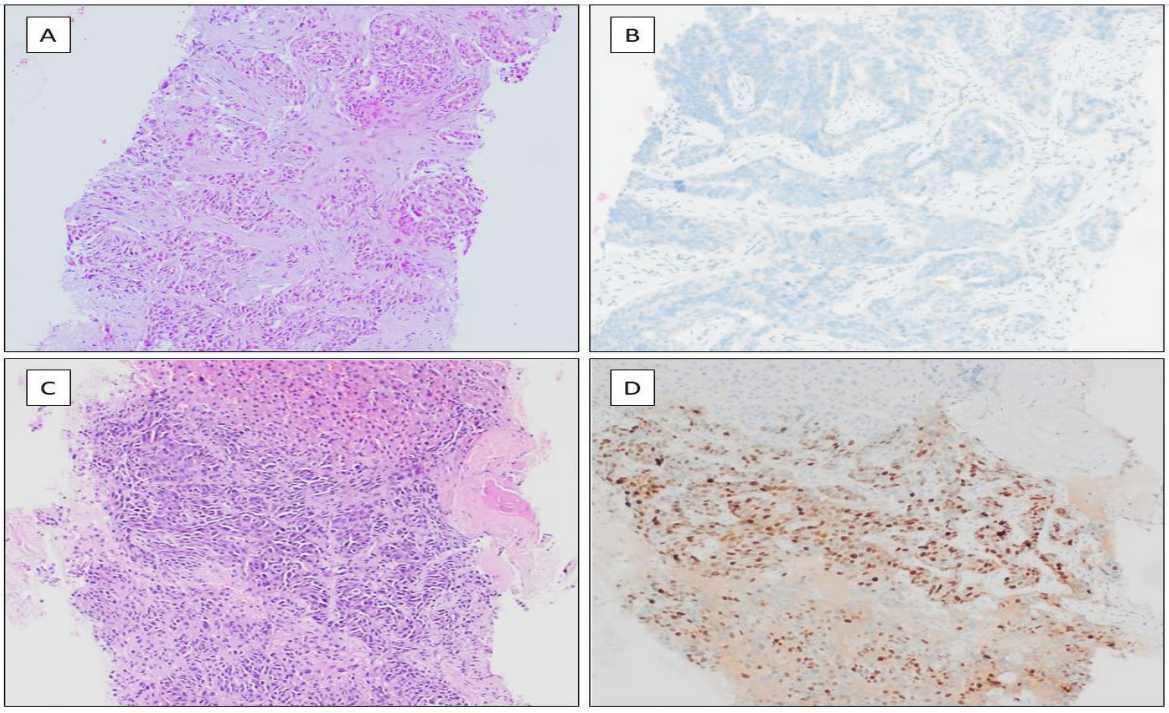

Figure 3. Breast biopsy of case number 45 (A; H&E, x100) and PR negativity in the primary tumor (B; x100); liver biopsy of the same case (C; H&E, x100) and 60% PR positivity in the metastatic tumor (D; x100)

Table 1. The number of cases with discordance and concordance for ER, PR, HER2, and Ki-67, as well as discordance rates

	Discordance			Concordance			
Biomarker	**Positive/ Negative**	**Negative/ Positive**	**Overall**	**Positive/ Positive**	**Negative/ Negative**	**Overall**	**Discordance Rate**
ER (57)	4 (7.0%)	1 (1.8%)	5 (8.8%)	45 (78.9%)	7 (12.3%)	52 (91.2%)	8.8% (p=0.0001)
PR (57)	18 (31.6%)	4 (7.0%)	22 (38.6%)	14 (24.6%)	21 (36.8%)	35 (61.4%)	38.6% (p=0.043)
HER2 (57)	3 (5.3%)	2 (3.5%)	5 (8.8%)	8 (14.0%)	44 (77.2%)	52 (91.2%)	8.8% (p=0.0001)
Biomarker	**High/Low**	**Low/High**	**Overall**	**High/High**	**Low/Low**	**Overall**	**Discordance Rate**
Ki-67 (45)	7 (15.6%)	6 (13.3%)	13 (28.9%)	31 (68.9%)	1 (2.2%)	32 (71.1%)	28.9% (p=1.000)

p-values calculated using the Fisher's exact test for categorical discordance

When comparing the HER2 levels between primary and metastatic tissues, an increase in HER2 was observed in 8 cases (14.0%), a decrease in 14 cases (24.6%), and no change in 35 cases (61.4%) (Figure 4). In the group analysis regarding HER2 positivity, 2 cases (3.5%) changed from HER2-negative to HER2-positive, while 3 cases (5.3%) changed from HER2-positive to HER2-negative. Accordingly, the discordance rate for HER2 was calculated as 8.8% (Table 1). The kappa test for concordance analysis showed good concordance between HER2 levels (kappa=0.708, p=0.0001). This suggests that HER2 levels are largely consistent between primary and metastatic tissues. Finally, to determine whether the change in HER2 values was statistically significant, Fisher's exact test was applied, and the change was found to be statistically significant (p=0.0001). This result indicates that the change in HER2 between the two biopsies is not randomly distributed and exhibits a significant difference.

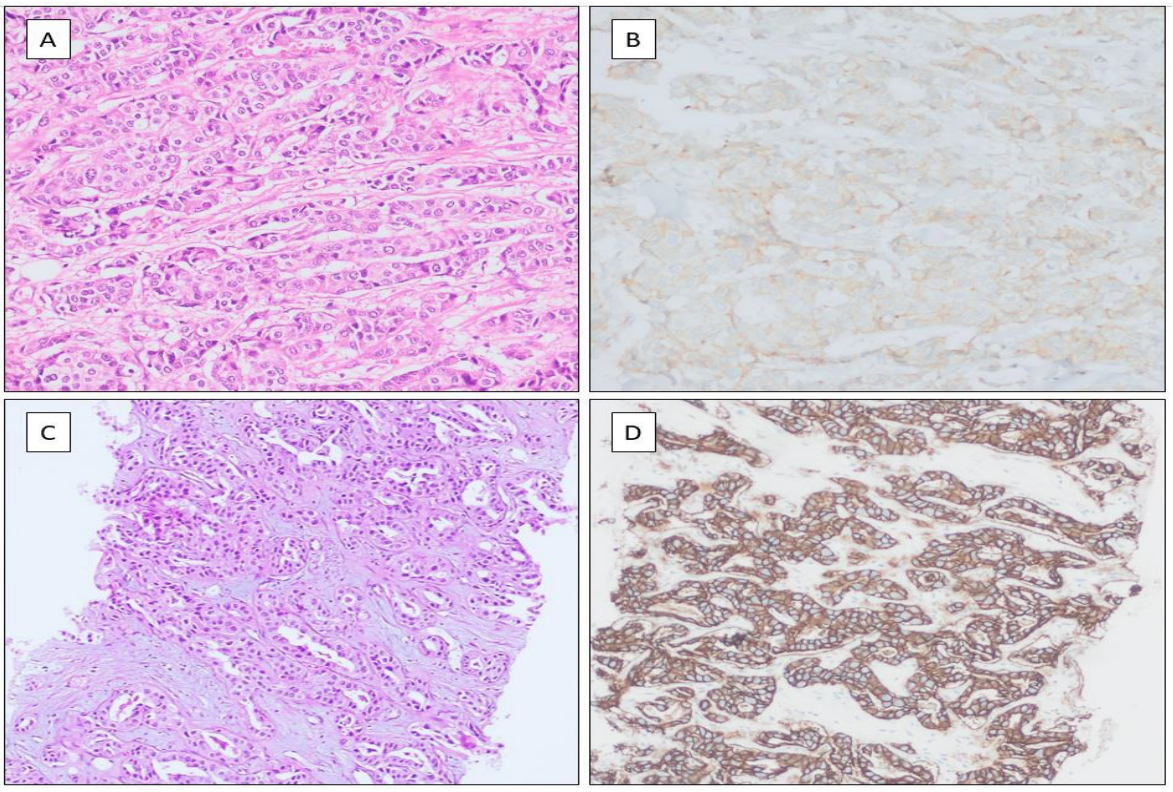

Figure 4. Breast biopsy of case number 10 (A; H&E, x200) and 1+ HER2 staining in the primary tumor (B; x200); liver biopsy of the same case (C; H&E, x100) and 3+ HER2 staining in the metastatic tumor (D; x200)

When evaluating the Ki-67 proliferation index between the two biopsies, an increase in Ki-67 was found in 24 cases (53.3%), a decrease in 16 cases (35.6%), and no change in 5 cases (11.1%). However, the analysis indicated that these changes were not statistically significant (Wilcoxon test; Z=-1.582, *p*=0.114). Similarly, the Friedman test indicated no significant difference in Ki-67 levels between primary tumors and metastatic tissues (χ^2=1.600, *p*=0.206). When the cases were grouped as Ki-67-low and Ki-67-high, it was observed that 6 cases (13.3%) changed from the Ki-67-low group to the Ki-67-high group, and 7 cases (15.6%) changed from the Ki-67-high group to the Ki-67-low group. Accordingly, the discordance rate for Ki-67 was calculated as 28.9% (Table 1). The kappa test showed that the concordance between Ki-67 levels was very weak and statistically insignificant (kappa=-0.039, *p*=0.793). Finally, to determine whether the change in Ki-67 values was statistically significant, Fisher's exact test was applied, and it was found that the change was not statistically significant (*p*=1.000). These findings suggest that the observed changes in Ki-67 levels between primary and metastatic tissues are likely due to biological variability rather than a systematic pattern.

Discussion

The discrepancy in hormone receptor status between primary breast cancers and their metastases was initially observed in the late 1970s and has since been the subject of extensive research [12]. Reported discordance rates in the literature vary widely, ranging from 0% to 78%, leading to significant discussion on the topic [5]. However, most studies are based on relatively small cohorts, typically involving fewer than 100 cases [7], while larger-scale studies are predominantly meta-analyses of previously published data. The variability in discordance rates across studies may be partly attributed to the small sample sizes in individual studies. In a study by Chen et al. [5] analyzing 390 cases from a single center, the discordance rates for ER, PR, and HER2 in metastatic breast carcinoma were found to be 18.3%, 40.3%, and 13.7%, respectively. In our study, the discordance rates for ER, PR, HER2, and Ki-67 were 8.8%, 38.6%, 8.8%, and 28.9%, respectively.

Several factors may contribute to the broad range of reported discordance rates. Biomarkers can be assessed using core needle biopsies, fine needle aspiration, or surgical resection materials from either primary or metastatic carcinomas, leading to potential false results due to tumor heterogeneity. Additionally, bone metastases are commonly included in studies, and the decalcification procedures used for these specimens can reduce the reliability of biomarker expression. Furthermore, the use of cytological samples, which may yield less reliable biomarker results, could also contribute to inconsistencies in findings. To minimize these confounding factors, our study exclusively included liver biopsies, excluding bone metastases and cytological materials, ensuring a more homogeneous sample set. Another factor influencing discordance rates may be variation in tissue fixation and processing methods. Different fixation solutions or tissue processing techniques can introduce inconsistencies in biomarker expression. However, in our study, all cases were fixed with formalin and underwent standardized tissue processing. Additionally, variability in IHC/ISH procedures and potential misinterpretation of biomarkers as false negative or false positive results may contribute to discrepancies.

To mitigate this, we employed standardized and validated staining protocols, testing all markers with both positive and negative control tissues. Moreover, all markers were evaluated by at least two pathologists, including at least one experienced breast pathologist, minimizing inter-observer variability. Notably, in the evaluation of ER expression, a discrepancy was observed between the Wilcoxon and Fisher's exact test results. While the Wilcoxon test did not demonstrate statistical significance when comparing continuous ER expression levels (*p*=0.322), the Fisher's exact test revealed a significant difference when ER status was analyzed categorically as positive or negative (*p*=0.0001). This divergence is attributable to the fundamental differences between the tests: the Wilcoxon test assesses numerical shifts in continuous variables, whereas the Fisher's exact test evaluates transitions between categorical classifications. This highlights the importance of considering both continuous and categorical perspectives in biomarker analysis, especially

when clinical decisions depend on threshold-based classifications. Despite these efforts to control for technical and methodological factors, receptor discordance remains a significant phenomenon. Previous studies have shown that discrepancies in receptor status are not solely attributable to methodological differences but instead reflect true biological changes in tumor progression [7, 13]. Our study supports this perspective, as our discordance rates align with previous findings and persist even after methodological standardization.

The majority of hormone receptor changes occur as a shift from positive to negative status. This can primarily be explained by the targeted elimination of cancer cells overexpressing ER or HER2 via endocrine or HER2-specific treatments. Although some studies, including ours, have also reported transitions from negative to positive status [5]. Metastasis, occurring during tumor progression, follows a clonal and selective pathway [14]. Studies indicate that genetically distinct subpopulations coexist within a tumor, each possessing different metastatic capabilities and biomarker expression profiles [15, 16]. This theory is further supported by the observation that receptor status is not stable throughout tumor progression, as evidenced by discordant receptor profiles between different metastatic sites in patients with multiple organ metastases [5]. Based on these findings, it is believed that a hormone receptor-positive clone within the tumor may develop metastatic capacity, leading to a shift in receptor status in metastases. Elevated Ki-67 levels indicate treatment failure or the need for an adjustment in the treatment regimen [17]. Ki-67 is widely recognized as an important prognostic marker in breast cancer, with elevated levels often associated with increased tumor aggressiveness and poorer outcomes. Previous studies, including large population-based analyses, have confirmed the prognostic relevance of Ki-67 expression in both primary and metastatic settings [18]. Furthermore, standardized assessment guidelines have been established by international working groups to improve consistency and clinical applicability [19]. In our study, although Ki-67 discordance did not reach statistical significance, nearly one-third of cases demonstrated shifts between low and high proliferation indices, further supporting the need for re-evaluation in metastatic lesions. Given the prognostic significance of Ki-67 expression, evaluating its status in metastatic biopsies may provide valuable insights into treatment efficacy and guide therapeutic modifications.

In conclusion, biomarker transformation is a well-documented phenomenon in breast cancer progression, significantly impacting treatment decisions and patient outcomes. Receptor status changes, whether from positive to negative or vice versa, have critical clinical implications, as they may result in ineffective treatment due to receptor loss or missed opportunities for targeted therapy. Given the dynamic nature of biomarker expression, reassessment of biomarkers in metastatic sites is essential to optimize treatment strategies and ensure patients receive the most effective targeted therapies based on real-time tumor biology. Implementing standardized protocols for biomarker evaluation and considering tumor heterogeneity when making treatment decisions are crucial steps in improving patient outcomes in metastatic breast cancer.

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Conflict of interest: No conflict of interest was declared by the authors.

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