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Original Research Paper

Histological and biomarker concordance between core needle biopsy and excision specimens in breast carcinoma

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Abstract: Core needle biopsy is commonly used to diagnose breast cancer and to assess important tumour markers before surgery. However, the results obtained from biopsy samples do not always match those from the final excision specimen, especially for markers related to tumour proliferation. **Methods:** In this study, we compared histological and biomarker findings between core needle biopsy and excision specimens in fifty patients with breast carcinoma. Estrogen receptor and Ki-67 were assessed by immunohistochemistry, and the expression of *ESR1*, *MKI67*, and *TOP2A* was analysed using real-time PCR. **Results:** Estrogen receptor results were largely similar between biopsy and excision specimens, and *ESR1* gene expression showed no relevant difference between the two sample types. In contrast, Ki-67 results varied considerably, with higher expression of proliferation-related genes seen in excision specimens. **Conclusion:** These findings suggest that estrogen receptor assessment on biopsy material is reliable, while evaluation of tumour proliferation may be affected by sampling differences. Additional molecular analysis may help in interpreting proliferation markers in routine practice.

Keywords: Breast carcinoma; Histology; Estrogen receptor; Ki-67; ESR1

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide and continues to be a major cause of cancer-related death [1, 2]. Accurate pathological assessment at the time of diagnosis is important because it influences prognosis and helps guide treatment decisions, especially in hormone receptor–positive disease [3, 4]. Core needle biopsy (CNB) is now widely used as the first diagnostic procedure for breast lesions, as it is less invasive than surgical excision and allows earlier evaluation of tumour histology and biomarkers [5]. Using CNB, information on tumour type, grade, and key immunohistochemical markers, including estrogen receptor (ER), can be obtained before definitive surgery, which is particularly relevant for planning endocrine therapy [6].

Many studies have examined the reliability of CNB for assessing hormone receptor status, especially ER, and most have reported good agreement between biopsy and excision specimens [7, 8]. These findings support the routine use of CNB in preoperative assessment. In contrast, evaluation of proliferation markers such as Ki-67 remains problematic. Differences in staining methods, scoring approaches, and tissue sampling contribute to considerable variability between laboratories and specimen types [9, 10]. A systematic review comparing Ki-67 results between CNB and excision specimens reported a wide range of concordance, suggesting that both technical factors and tumour heterogeneity may limit reliable interpretation [11]. Since Ki-67 is commonly used to help distinguish between luminal A and luminal B breast cancer subtypes, inconsistent results may have important clinical consequences [10].

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In everyday clinical practice, immunohisto-chemical findings obtained from CNB are often used to guide neoadjuvant and adjuvant treatment decisions. However, disagreement between biopsy and excision results may lead to incorrect subtype classification or suboptimal therapy selection [12, 13]. Gene expression analysis has been suggested as a complementary approach to immunohistochemistry, as transcripts such as ESR1, MKI67, and other proliferation-related genes can provide additional information at the mRNA level [14]. Assessing both protein expression and gene expression may help determine whether observed differences reflect sampling limitations or true biological variation within the tumour. Although interest in improving breast cancer biomarker assessment is increasing, relatively few studies have combined gene expression analysis with direct histopathological comparison of CNB and excision specimens in clinical settings. In the present study, we compare ER status and Ki-67 index between CNB and excision samples and further examine the transcriptional behaviour of ESR1, MKI67, and TOP2A to evaluate their consistency across sampling methods. This approach aims to improve understanding of biomarker concordance and its implications for reproducible breast cancer evaluation.

2. Methodology

Study Design and Case Selection

This investigation was conducted as a single-centre, cross-sectional analytical study involving patients diagnosed with primary breast carcinoma. Fifty female patients presenting with a clinically palpable breast lump were consecutively included. In all cases, the diagnosis of malignancy was confirmed by histopathological examination. Only patients who underwent both preoperative core needle biopsy (CNB) and subsequent surgical excision of the tumour were eligible for inclusion, allowing direct comparison between the two specimen types. Patients who had received neoadjuvant chemotherapy prior to surgery were excluded to avoid treatment-related alterations in histological features and biomarker expression. Non-neoplastic breast lesions, as well as cases with inadequate tissue for immunohistochemical or molecular analyses, were also excluded from the study. Relevant clinical and pathological information, including patient age, presenting symptoms, tumour laterality, histological subtype, and tumour grade, was obtained from institutional medical records. All data were anonymised prior to analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committees of the University of Fallujah and Al-Yarmook Teaching Hospital.

Histopathological Evaluation

All core needle biopsy and surgical excision specimens were fixed in formalin and processed using routine histopathological procedures. In the case of core needle biopsies, all available tissue cores were submitted for processing to ensure adequate representation of the lesion. For excision specimens, gross examination was first performed, and representative areas containing tumour were selected for further evaluation. Formalin-fixed, paraffin-embedded tissue blocks were cut into thin sections measuring approximately 4–5 μm and stained with haematoxylin and eosin for routine microscopic examination. Tumour type was identified according to the World Health Organization classification for breast tumours. Grading was carried out using the Nottingham system, based on assessment of glandular formation, nuclear features, and mitotic activity, as routinely applied in diagnostic practice. Histopathological assessment of core needle biopsy and excision specimens was performed independently. Tumour type and grade identified on CNB were subsequently compared with those obtained from the corresponding excision specimens in order to assess the level of concordance between the two sampling methods.

Immunohistochemical Analysis

Immunohistochemical evaluation of estrogen receptor (ER) and Ki-67 was performed on formalin-fixed, paraffin-embedded tissue sections derived from both core needle biopsy and excision specimens. Sections measuring 4–5 μm in thickness were prepared and mounted on positively charged slides, followed by overnight incubation at 60 °C to ensure adequate tissue adherence. Sections were deparaffinised in xylene and rehydrated through a graded series of alcohols. Antigen retrieval was carried out using citrate buffer at alkaline pH (pH 8.0–9.0) under heat-induced conditions in a

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microwave oven. Endogenous peroxidase activity was quenched by treatment with hydrogen peroxide for 15–20 minutes. Primary antibody incubation was then performed using monoclonal mouse anti-human antibodies directed against estrogen receptor (PathnSitu, catalogue no. R06042RA; dilution 1:100) and Ki-67 (PathnSitu, catalogue no. R06096UA; dilution 1:100). Slides were incubated with the primary antibodies for 90 minutes at room temperature. Detection was achieved using a polymer-based secondary antibody system, with visualisation performed using 3,3′-diaminobenzidine as the chromogen. Sections were subsequently counterstained with haematoxylin, dehydrated, cleared, and mounted. Estrogen receptor expression was assessed based on the presence of nuclear staining in tumour cells and categorised as positive or negative according to accepted immunohisto-chemical criteria. The Ki-67 proliferation index was determined by estimating the percentage of positively stained tumour cell nuclei in areas demonstrating the highest labelling density. A cut-off value of 20% was applied to classify Ki-67 expression as low (≤20%) or high (>20%). All immunohistochemical slides were evaluated by a pathologist who was blinded to the corresponding biopsy or excision findings in order to minimise observer bias.

Gene Expression Analysis

Gene expression analysis was carried out on paired core needle biopsy and excision specimens obtained from the same patients. Tumour-rich regions were first identified on corresponding haematoxylin and eosin–stained sections, and these areas were carefully selected from formalin-fixed, paraffin-embedded tissue blocks. Areas of necrosis and adjacent non-neoplastic tissue were deliberately avoided to minimise contamination. Total RNA was extracted using a commercially available kit optimised for paraffin-embedded tissues, following the manufacturer's instructions. The concentration and purity of the extracted RNA were assessed spectrophotometrically, and only samples of acceptable quality were used for subsequent analysis. Complementary DNA (cDNA) synthesis was performed using a reverse transcription kit under standard reaction conditions, with equal amounts of RNA used for all samples to ensure consistency. Quantitative real-time polymerase chain reaction (qRT-PCR) was then performed to evaluate the expression of ESR1, MKI67, and the proliferation-associated gene TOP2A. Gene-specific primers were used for amplification, and reactions were carried out using a SYBR Green–based master mix on a real-time PCR platform. All reactions were performed in duplicate to improve reliability. Gene expression levels were normalised against an internal housekeeping gene, and relative expression was calculated using the comparative cycle threshold (ΔΔCt) method. Expression values obtained from core needle biopsy samples were directly compared with those from the corresponding excision specimens to assess differences related to sampling method.

Statistical Analysis

The data were analysed using IBM SPSS Statistics (version 27.0). Categorical data were described using simple counts and percentages. Agreement between core needle biopsy and excision specimens for immunohistochemical results was assessed using Cohen's kappa statistic, and the level of agreement was interpreted using commonly accepted criteria. For the gene expression results, paired comparisons between biopsy and excision samples were analysed using two-way analysis of variance, with Šidák's correction applied to account for multiple comparisons across the different genes. The ability of core needle biopsy to predict ER and Ki-67 status was further assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value, taking the excision specimen as the reference. All analyses were two-sided, and a p value below 0.05 was taken as statistically significant.

3. Results and discussion

Demographics and Clinico-pathologic Characteristics

The demographic and clinico-pathologic characteristics of the study cohort are summarised in Table 1. The mean age of the patients was 50 years, with the majority of cases occurring in the 41–60 year age group, which comprised 62% of the study population. Tumour laterality showed a near-equal distribution, with right-sided involvement in 52% of patients and left-sided involvement in 48%. One patient was found to have bilateral disease. A palpable breast lump was the

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presenting complaint in all patients at the time of clinical assessment. Other associated symptoms were reported less frequently and included breast pain in 14% of cases, skin ulceration in 10%, puckering of the skin in 8%, nipple retraction in 4%, and nipple discharge in 4%.

Table 1. Clinicopathological character-istics of the study cohort

Variable	Category	CNB, n (%)	Excision, n (%)
Age group (years)	< 41	9 (17)	—
	42–59	30 (61)	—
	> 59	12 (21)	—
Breast side involved	Left	25 (47)	—
	Right	25 (51)	—
Presenting features*	Palpable lump	51 (101)	—
	Breast pain	8 (15)	—
	Skin changes / others	12 (25)	—
Molecular subtype	Luminal A	20 (39)	—
	Luminal B (HER2–)	6 (15)	—
	Luminal B (HER2+)	8 (13)	—
	HER2-positive (non-luminal)	7 (13)	—
	Triple-negative	12 (23)	—
Tumour type on histology	Invasive ductal carcinoma	29 (62)	25 (47)
	Invasive lobular carcinoma	16 (31)	11 (21)
	Less common subtypes†	6 (11)	17 (30)
Histological grade (Nottingham)	Grade 1	7 (13)	7 (11)
	Grade 2	22 (43)	20 (43)
	Grade 3	24 (47)	24 (47)

Histopathological evaluation was performed according to the College of American Pathologists protocol and the WHO 2012 classification. Invasive ductal carcinoma was the most common histological subtype identified in both core needle biopsy and excision specimens, representing 60% and 48% of cases, respectively. Invasive lobular carcinoma was the next most frequent subtype, observed in 30% of CNB specimens and 20% of excision specimens. A small proportion of cases demonstrated less common histological variants, including pleomorphic lobular carcinoma, invasive carcinoma with medullary or apocrine features, as well as metaplastic and mucinous carcinoma (Figures 1A and 1B).

Tumour grading using the Nottingham grading system indicated a predominance of high-grade disease. Grade 3 tumours were most frequently identified in both CNB (59%) and excision specimens (46%). Grade 2 tumours accounted for 29% of CNB specimens and 42% of excision specimens, while grade 1 tumours constituted 12% of cases in both specimen types. Immunohisto-chemical based molecular classification revealed luminal A as the most prevalent subtype, identified in 38% of patients. This was followed by triple-negative breast cancer (22%), luminal B (HER2-negative) and luminal B (HER2-positive) subtypes (14% each), and HER2-positive non-luminal tumours (12%).

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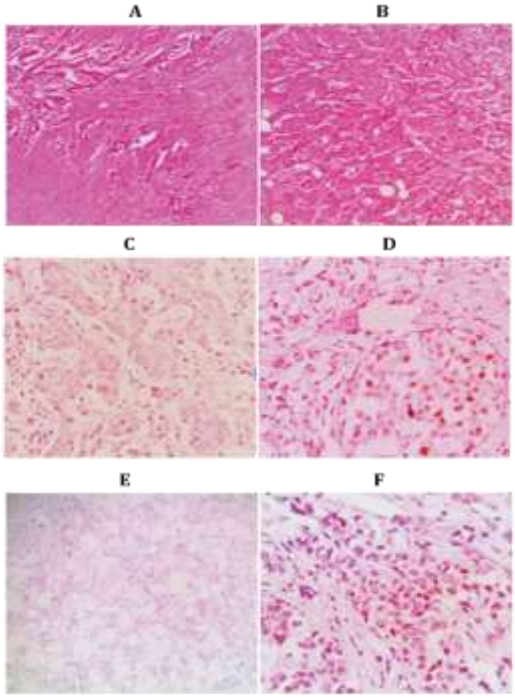

Fig1: Histological and immunohisto-chemical features of invasive ductal carcinoma, not otherwise specified. (A, B) Haematoxylin and eosin–stained sections showing tumour cells arranged in ductal structures as well as solid nests and trabeculae (×100). (C–F) Estrogen receptor immunostaining demonstrating absent to variable nuclear positivity, corresponding to Allred scores 0, 3 (1+2), 3 (2+1), and 4 (3+1).

ER Status and Ki-67 Index in Breast Carcinoma

Immunohistochemical analysis showed estrogen receptor positivity in 26 cases (52%) on core needle biopsy and in 33 cases (66%) on the corresponding excision specimens. In contrast, ER negativity was identified in 24 CNB samples (48%) and 17 excision specimens (34%) (Figure 1C–F; Table 2). A discrepancy in ER status between CNB and excision specimens was observed in seven patients, with invasive ductal carcinoma, not otherwise specified, representing the most frequent histological subtype among these discordant cases (n = 4) (Table 1).

Table 2: Immunohistochemical analysis of ER status and Ki-67 index in breast carcinoma

Marker	Category	CNB, n (%)	Excision, n (%)	Agreement (%)	κ value	p value
Estrogen receptor	Positive	27 (51)	32 (65)	87	0.715	<0.001
	Negative	23 (49)	18 (35)			
Ki-67 index	≤20 %	31 (62)	26 (52)	53	0.081	0.7734
	>20 %	19 (39)	24 (51)			

Evaluation of the Ki-67 proliferation index demonstrated low expression in 30 CNB samples (60%) and in 25 excision specimens (50%). High Ki-67 expression was detected in 20 CNB samples (40%) and 25 excision specimens (50%) (Table 2). Overall, 23 cases exhibited discordance in Ki-67 index between CNB and excision specimens, the majority of which were invasive ductal carcinoma NOS (n = 14) (Table S2; Figure 2A–F). A Ki-67 cut-off value of ≤20% was applied to define low proliferative activity, while values exceeding 20% were classified as high, allowing stratification into luminal A and luminal B molecular subtypes. Agreement between CNB and excision specimens was evaluated using Cohen's kappa statistics. A strong and statistically significant concordance was observed for ER status ($\kappa > 0.6$, $p < 0.0001$), whereas no statistically significant agreement was identified for the Ki-67 index (Table 2). The diagnostic performance of CNB relative to excision specimens, including sensitivity, specificity, positive predictive value, and negative

predictive value for both ER and Ki-67, is presented in Table 3. Overall, ER assessment demonstrated higher diagnostic accuracy compared with evaluation of the Ki-67 index.

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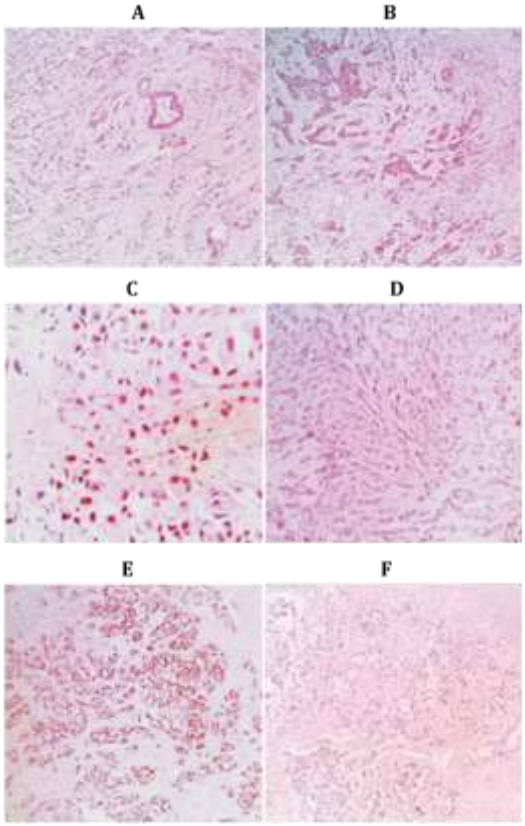

Fig 2: Immunohistochemical staining patterns in breast carcinoma. (A–E) Estrogen receptor staining showing variable nuclear positivity with Allred scores of 5 (3+2), 6 (4+2), 7 (4+3), 7 (5+2), and 8 (5+3). (F) Section showing high Ki-67 expression, with positive staining in approximately 75% of tumour cell nuclei.

Differential expression of estrogen receptor and proliferation-associated genes in core needle biopsy and excision specimens

Quantitative real-time PCR was used to compare gene expression between paired core needle biopsy and excision specimens (Figure 3). Expression levels of ESR1, MKI67, and TOP2A were examined to see whether the immunohistochemical findings were reflected at the mRNA level. For ESR1, expression was similar in biopsy and excision samples, and no statistically significant difference was found between the two groups (adjusted p = 0.9934) (Figure 3). This suggests that estrogen receptor expression remained stable regardless of the type of specimen analysed.

In contrast, higher expression levels were observed for the proliferation-related genes MKI67 and TOP2A in excision specimens when compared with the matched biopsy samples. The increase in MKI67 expression was statistically significant (p = 0.0015), and a similar finding was noted for TOP2A (p = 0.0004) after adjustment for multiple comparisons (Figure 3). These results indicate that proliferation-related gene expression was more prominent in excision specimens than in biopsy material. Overall, the gene expression findings follow the same trend seen with immunohistochemistry, showing stable estrogen receptor expression but greater variability in markers related to tumour proliferation.

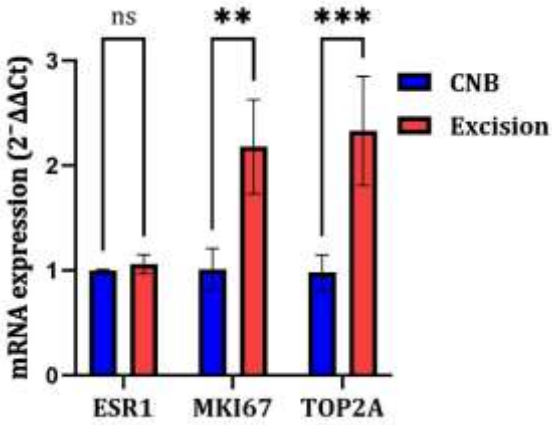

Fig **3:** Gene expression levels in paired core needle biopsy and excision specimens from breast carcinoma cases. Relative expression of ESR1, MKI67, and TOP2A was calculated using the $2^{-}\Delta\Delta Ct$ method after normalisation to a housekeeping gene. Data are shown as mean ± standard deviation. No difference was observed for ESR1 expression between specimen types (p = 0.9934), whereas MKI67 (p = 0.0015) and TOP2A (p = 0.0004) were higher in excision specimens. ns, not significant.

In this study, we compared estrogen receptor status and Ki-67 proliferation index between core needle biopsy and surgical excision specimens, and also examined whether gene expression analysis could help explain the differences observed. Overall, the results point to a clear difference between the behaviour of hormone receptor markers and proliferation markers when different sampling methods are used.

Estrogen receptor assessment showed good agreement between biopsy and excision specimens, supported by the kappa analysis and diagnostic performance results. This finding is in line with earlier studies reporting that ER evaluation on core needle biopsy is generally reliable and can be used with confidence in routine clinical

practice [5, 15, 16]. The gene expression results in the present study further support this observation. ESR1 mRNA levels were similar in paired biopsy and excision samples, suggesting that estrogen receptor expression is relatively stable within the tumour and is not markedly influenced by sampling method. Taken together, these findings indicate that ER status can be consistently assessed at both the protein and transcript levels.

In contrast, assessment of tumour proliferation showed a different pattern. The Ki-67 index demonstrated considerable discordance between core needle biopsy and excision specimens, with low agreement and reduced diagnostic performance. Similar variability in Ki-67 assessment has been reported previously, particularly when analysis is based on limited biopsy material [17-19]. One likely explanation is tumour heterogeneity, as proliferative activity may vary across different tumour areas. Small biopsy samples may therefore miss regions with higher proliferation, leading to underestimation of Ki-67 expression [20].

The gene expression findings provide further insight into this issue. While ESR1 expression remained stable, the proliferation-related genes MKI67 and TOP2A were expressed at higher levels in excision specimens compared with paired biopsy samples. This suggests that the differences seen with Ki-67 immunohistochemistry are not only technical but may also reflect genuine biological variation within the tumour. Comparable results have been described in studies examining gene expression differences between biopsy and excision specimens, particularly for genes involved in cell cycle activity and proliferation [21, 22].

Correct classification of luminal A and luminal B breast cancer subtypes is clinically relevant, as these subtypes differ in prognosis and treatment response. Although Ki-67 is commonly used as a surrogate marker of proliferation in routine reporting, its variability may lead to subtype misclassification when decisions are based solely on biopsy findings [23, 24]. The results of the present study support previous recommendations advising caution when interpreting Ki-67 values obtained from core needle biopsy, especially in situations where treatment planning relies heavily on proliferation status [25]. This study has several strengths, including the use of paired biopsy and excision specimens from the same patients and the combination of immunohistochemical and gene expression analyses. However, some limitations should be considered. The study was performed at a single centre with a relatively small number of cases, and molecular analysis was limited to selected genes rather than a broader transcriptomic approach. Future work involving larger patient cohorts and more extensive sampling may help clarify the clinical impact of intratumoural heterogeneity in breast cancer [14, 26, 27].

Conclusion

In summary, the findings of this study indicate that estrogen receptor assessment on core needle biopsy is generally reliable, whereas evaluation of tumour proliferation using Ki-67 is more variable. The stability of ESR1 expression at both the protein and mRNA levels contrasts with the variability observed for proliferation-associated genes. These results highlight the need for careful interpretation of Ki-67 results obtained from biopsy material and suggest that complementary molecular analysis may improve the reliability of breast cancer biomarker assessment in clinical practice.

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