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The Reliability of Core-Needle Biopsy in Assessment of Hormone Receptor, HER2, and Ki-67 in Breast Carcinoma

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Objective: The purpose of this study was to compare the estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) status and Ki-67 index by immunohistochemical (IHC) analysis in breast carcinoma to determine the level of concordance between core-needle biopsy (CNB) and surgical specimens.

Summary of Background: Accurate preoperative diagnosis of a breast lesion has recently been considered essential to the treatment strategy to achieve optimal treatment without delay. However, the reliability of using CNB specimens for IHC assessment is in relatively small number of cases and differing results between previous studies.

Methods: The patients included in this study were 255 patients with primary breast carcinoma who had CNB and subsequent surgical resection at the Hospital of Dokkyo Medical University between 2010 and 2016. We compare the ER, PgR, HER2 status, and Ki-67 index by IHC analysis in breast carcinoma between CNB and surgical specimens.

Results: There was a concordance rate between the ER, PgR, HER2, and Ki-67 IHC assessment of CNB and surgical specimens in 99.0%, 92.1%, 86.3%, and 91.5%, respectively. We also found small numbers of discordant cases in the estimation for which a discrepancy in determination led to a change in treatment.

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Conclusions: Our results do not entirely invalidate the use of CNB for assessment if they are the only source of tumor tissue available, but suggest a more cautious approach in their interpretation when clinical decisions are being made.

Key words: Hormone receptor – HER2 – Ki-67 – Core-needle biopsy – Surgical specimens

The role of core-needle biopsy (CNB) has become well established as an important diagnostic tool for breast carcinoma.[1–3] CNB is less invasive than excision biopsy and generally provides more reliable information, especially architectural and histologic information. Accurate preoperative diagnosis of a breast lesion has recently been considered essential to the treatment strategy to achieve optimal treatment without delay. Cases receiving preoperative systemic therapy have increased to reduce the tumor volume and eliminate possible micro metastasis for patients with locally advanced breast carcinoma. Therefore, there are clinical demands on pathologists to provide not only a histologic diagnosis, but also prognostic information for patients, including the determination of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki-67 index for treatment.[4,5] ER is a powerful predictive factor of response to endocrine treatment with tamoxifen or aromatase inhibitors and long-term outcome.[6–8] Similarly, HER2 overexpression has been associated with poor prognosis in breast carcinoma and is a determinant of response to trastuzumab and a possible marker of resistance to certain endocrine and chemotherapy treatments.[9–11] Ki-67 is a nuclear protein of unclear function present in all proliferating cells and breast carcinomas expressing high levels of Ki-67 are associated with poor prognosis.[12–18] Although widely used as a predictive marker in neo-adjuvant breast cancer studies, less is known about Ki-67 expression between CNBs and their corresponding surgical specimens. Further, gene expression studies have identified molecular subtypes of breast carcinoma that have prognostic value across multiple treatment settings. To date, immunohistochemical (IHC) analysis of ER, PgR, HER2 status, and Ki-67 index has been considered a surrogate marker in identifying molecular subtypes of breast carcinoma.[19] However, the reliability of using CNB specimens for detailed assessment is in doubt because of the relatively small number of cases and differing results between previous studies (Table 1).[20–33] The purpose of this study was to compare the ER, PgR, HER2 status, and Ki-67 index by IHC analysis in breast carcinoma to determine the level of concordance between CNB and surgical specimens.

Patients and Methods

The patients included in this study were 255 patients with primary breast carcinoma who had CNB and subsequent surgical resection at the Hospital of Dokkyo Medical University between 2010 and 2016. For each case, all available hematoxylin and eosin–stained sections were reviewed to confirm the diagnosis of mammary disease with no knowledge of either prior histologic results or clinical outcomes. Patients were included only if both CNB and surgical specimens were available for the tumor. IHC analysis was performed using a fully automated system. Briefly, 5-μm-thick, unstained sections were placed onto an electrostatically charged glass slide and baked to allow for tissue adherence. The sections were deparaffinized and rehydrated in graded alcohol. For antigen retrieval, the sections were incubated with protease for 10 minute in chambers at 37°C. The sections were then taken to an automated stainer (VENTANA, BENCHMARK XT, Japan) following the vendor's protocol. The IHC-stained slides of each tumor were compared with positive and negative controls. All antibodies were prediluted and provided by Roche and DAKO Inc. (Japan) Specimens were judged to be positive for ER (Roche, clone SP1) and PgR (Roche, clone 1E2) when at least 1% of the nuclei in the tumor cells stained positively (Fig. 1a and 1b).[34] HER2 (Roche, clone 4B5) evaluation was done with 224 cases, excluding noninvasive carcinoma, diagnosed by CNB or surgical specimens. Tumor cells were considered positive for HER2 if they showed complete and intense circumferential membrane staining, and if >10% of tumor cells in an invasive area were scored +3 as positive (Fig. 1c).[35] In addition, the Ki-67 (Dako, clone Mib-1) index measured the percentage of breast carcinoma cell nuclei that were high expression, with a cutoff for analysis of >14% (Fig. 1d).[19] We compare the ER, PgR, HER2 status, and Ki-67 index by IHC analysis

Table 1 Summary of previous studies testing concordance rates between CNB and surgical specimens

Article	Year	No. of cases	Concordance (%)			
			ER	PgR	HER2	Ki-67
Mann *et al*[20]	2005	100	86	83	80	—
Cavaliere *et al*[21]	2005	68	61.7	61.5	89.7	—
Burge *et al*[22]	2006	87	95	89	96	—
Cahill *et al*[23]	2006	95	70	72	64	—
Usami *et al*[24]	2007	112(60*)	95	88	88	—
Sutela *et al*[25]	2008	41	83	88	93	—
Park *et al*[26]	2009	104	99	97.1	86.5	—
Arnedos *et al*[27]	2009	336	98.2	85	98.8	—
Tamaki *et al*[28]	2010	353(225*)	91.1	88.6	85.6	—
Ough *et al*[29]	2011	209	88	78	81	—
Ricci *et al*[30]	2012	69	95	95	95	95
Chen *et al*[31]	2013	298	93.6	85.9	96.3	79.5
Seferina[32]	2013	526	89.5	82.5	80.6	—
Munch-Petersen[33]	2014	89	98	—	84	—
Current	2016	255(224*)	99.0	92.1	86.3	91.5

CNB, core needle biopsy; ER, estrogen receptor; PgR, progesterone receptor; HER2, Human epidermal growth factor receptor 2.

*Number of cases excluding noninvasive carcinoma.

in breast carcinoma between CNB and surgical specimens. Concordance analysis of hormone receptors, HER2 status, and Ki-67 index was done for CNB and surgical specimens using the χ^2 test. In all tests, a two-sided $P < 0.05$ was considered statistically significant.

Results

The clinicopathologic characteristics are summarized in Table 2. Two hundred fifty-five breast carcinomas were selected. Of these, 224 patients had a diagnosis of invasive carcinoma and 31 had noninvasive carcinoma. All patients were women, and their ages ranged from 31 to 91 years (mean, 59 years). The mean tumor size was 1 cm at the maximum diameter. Lymph node metastases were found in 55 cases. The Elston and Ellis modified Bloom-Richardson grades were I in 110 cases, II in 71 cases, and III in 43 cases of invasive carcinoma, whereas the nuclear grade was low in 15 cases, intermediate in 6 cases, and high in 10 cases of noninvasive carcinoma.

Analysis of the concordance of biomarkers between CNB and breast carcinoma surgical specimens

The concordance rates between CNB and surgical specimen are summarized in Tables 3–5. The concordance rate between the ER assessment of CNB and surgical specimen for invasive carcinoma

Table 2 Relationship between the clinicopathologic characteristics of breast carcinoma

Parameter	Total breast carcinoma (255 cases)	Invasive (224 cases)	Noninvasive (31 cases)
Mean age, y	59 (31–91)	59 (31–91)	60 (45–74)
Mean tumor size, cm	1 (0.2–10.5)	2.3 (0.5–12)	3.3 (0.3–11)
Lymph node status	55 (1–12)	55 (1–12)	0
Grading			
I (low)	125	110	15
II (intermediate)	77	71	6
III (high)	53	43	10

was 99.4%, for noninvasive carcinoma was 96.1%, and totally was 99.0% with a discrepancy only in 2 cases. The concordance rate between the PgR assessment of CNB and surgical specimen for invasive carcinoma was 91.6%, for noninvasive carcinoma was 95.4%, and totally was 92.1% with a discrepancy in 14 cases. HER2 status was not assessed in 31 cases of noninvasive breast carcinoma. The concordance rate between the HER2 assessment of CNB and surgical specimen for invasive carcinoma was 86.3% with a discrepancy in 3 cases. The concordance rate between the Ki-67 assessment of CNB and surgical specimen for invasive carcinoma was 96.5%, for noninvasive carcinoma was 62.5%, and totally was 91.5% with a discrepancy in 14 cases. There was no statistical difference in ER, PgR, HER2 status, and Ki-67 index concordance rate between CNB and surgical specimen.

For ER, 207 (81.2%) of the CNBs were scored as positive compared with 205 cases (80.4%) in the surgical specimens of all breast carcinoma cases. In invasive carcinomas, ER was positive in 181 (80.8%) of the CNB and 180 (80.3%) of the surgical specimens. In noninvasive carcinoma, ER was positive in 26 (83.9%) of the CNB and 25 (80.6%) of the surgical specimens.

For PgR, 178 cases (69.8%) of the CNB were scored as positive compared with 164 cases (64.3%) in the surgical specimens of all the breast carcinoma cases. In invasive carcinoma, PgR was positive in 156 (69.6%) of the CNB and 143 (63.8%) of the surgical specimens. In noninvasive carcinoma, PgR was positive in 22 (71.0%) of the CNB and 21 (67.7%) of the surgical specimens.

From the 224 invasive carcinoma patients, HER2 was positive in 22 (9.8%) of the CNB and 19 (8.5%) of the surgical specimens.

Ki-67 was scored as high expression in 165 (64.7%) of the CNB and 151 (59.2%) of the surgical

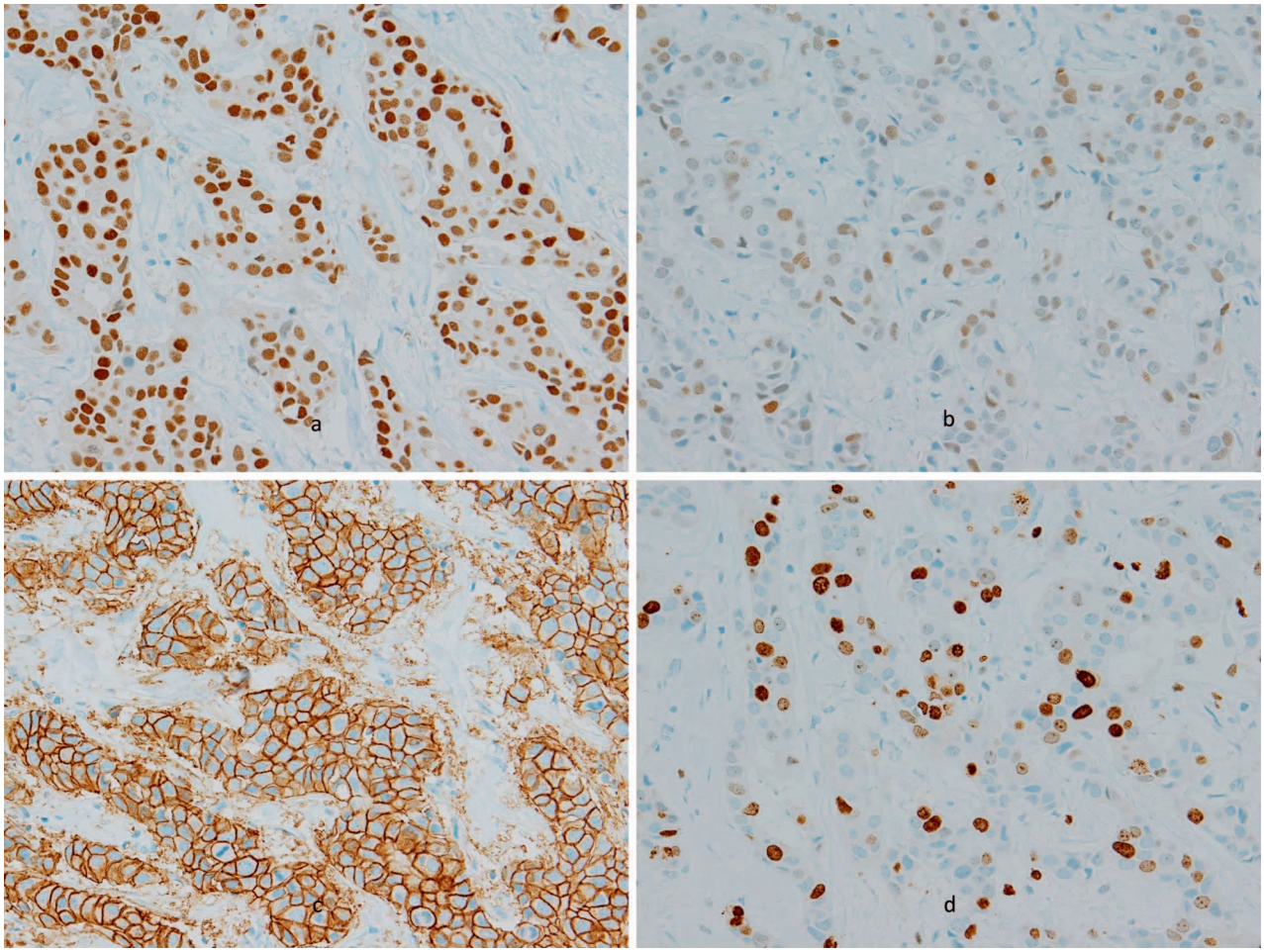

Fig. 1 Immunohistochemistry of the same tumor showing positivity for ER (a), PgR (b), HER2 (c), and Ki-67 (d) positive cells within a breast carcinoma (200×).

specimens of all the breast carcinoma cases. In invasive carcinomas, Ki-67 was scored as high expression in 149 (66.5%) of the CNB and 141 (62.9%) of the surgical specimens. Further, in noninvasive carcinomas, Ki-67 was scored as high expression in 16 (51.6%) of the CNB and 10 (32.3%) of the surgical specimens.

Discussion

CNB is widely used in routine preoperative practice to evaluate the nature of breast lesions.[1–3] For therapeutic choices in the treatment of breast carcinoma, CNB is a reliable method to provide information not only on the histologic diagnosis, but also on various predictive factors because such information is very important when deciding the therapeutic strategy.[4–11] In addition, breast carcinoma is a heterogeneous disease, and IHC analysis of ER, PgR, and HER2 status may be surrogate markers in molecular analysis by microarray.[19] There have been several studies on these markers' estimation accuracy and reliability between CNB and surgical specimens of breast carcinoma (Table 1).[20–33] ER and PgR showed a wide variation and the rates of concordance between CNB and surgical specimens were 61.7–99% and 61.5–97.1%, respectively. In our results, there were no statistically significant differences in ER and PgR expression between CNB and surgical specimens. However, we found that the concordance of PgR was lower than that of ER in all breast carcinoma cases (Table 3). Previous publications also suggested that the concordance rate between CNB and surgical specimens is lower for PgR than ER.[20–22,26–28,31] There are several explanations for these results. One explanation may be poorer fixation of surgical specimens

Table 3 Analysis of the concordance of biomarkers between CNB and surgical specimens of the breast carcinoma

	Surgical specimen				
Biomarkers	**Positive**	**Negative**	**Total**	**Concordance rate (%)**	***P* value**
CNB					
ER				99.0	0.8222
Positive	202	5	207 (81.2%)		
Negative	3	45	48 (18.8%)		
Total	205 (80.4%)	50 (19.6%)	255 (100%)		
PgR				92.1	0.1872
Positive	154	24	178 (69.8%)		
Negative	10	67	77 (30.2%)		
Total	164 (64.3%)	91 (35.7%)	255 (100%)		
HER2*				86.3	0.6230
Positive	13	9	22 (9.8%)		
Negative	6	196	202 (90.2%)		
Total	19 (8.5%)	205 (91.5%)	224 (100%)		
Ki-67				91.5	0.5207
Positive	121	44	165 (64.7%)		
Negative	30	60	90 (35.3%)		
Total	151 (59.2%)	104 (40.8%)	255 (100%)		

*Noninvasive carcinoma of the breast excluded.

compared with CNB specimens, including delayed fixation or under- or over-fixation with formalin prior to IHC analysis. This is because the PgR test seems to require a higher preparation quality than an ER test.[20] A second explanation for the discrepancy is the fact that PgR tends to be distributed more heterogeneously within the tumor. Zidan *et al* also indicated that this result is probably a reflection of the greater heterogeneity of PgR expression.[36] They reported that assessment of PgR in CNB is less reliable with an absolute agreement of only 42% and a partial agreement of 69% between the CNB and excisional biopsy specimen scores. Further, the observation that with modern IHC methods, breast carcinomas that are ER negative are often also PgR negative, so PgR testing is no longer useful in daily clinical decision making.[37] However, in recent reports, PgR status has been shown to be of value in predicting response to hormonal therapy.[38–40] Liu *et al* reported that PgR correlates with ER expres-

Table 4 Analysis of the concordance of biomarkers between CNB and surgical specimens of the 224 invasive carcinoma of the breast

	Surgical specimen				
Biomarkers	**Positive**	**Negative**	**Total**	**Concordance rate (%)**	***P* value**
CNB					
ER				99.4	0.9049
Positive	178	3	181 (80.8%)		
Negative	2	41	43 (19.2%)		
Total	180 (80.3%)	44 (19.7%)	224 (100%)		
PgR			156 (69.6%)	91.6	0.1924
Positive	134	22			
Negative	9	59	68 (30.4%)		
Total	143 (63.8%)	81 (36.2%)	224 (100%)		
HER2*				86.3	0.6230
Positive	13	9	22 (9.8%)		
Negative	6	196	202 (90.2%)		
Total	19 (8.5%)	205 (91.5%)	224 (100%)		
Ki-67				96.5	0.4289
Positive	113	36	149 (66.5%)		
Negative	28	47	75 (33.5%)		
Total	141 (62.9%)	83 (37.1%)	224 (100%)		

*Noninvasive carcinoma of the breast excluded.

Table 5 Analysis of the concordance of biomarkers between CNB and surgical specimens of the 31 noninvasive carcinoma of the breast

	Surgical specimen				
Biomarkers	**Positive**	**Negative**	**Total**	**Concordance rate (%)**	***P* value**
CNB					
ER				96.1	0.7396
Positive	24	2	26 (83.9%)		
Negative	1	4	5 (16.1%)		
Total	25 (80.6%)	6 (19.4%)	31 (100%)		
PgR				95.4	0.7830
Positive	20	2	22 (71.0%)		
Negative	1	8	9 (29.0%)		
Total	21 (67.7%)	10 (32.3%)	31 (100%)		
Ki-67				62.5	0.0961
Positive	8	8	16 (51.6%)		
Negative	2	13	15 (48.4%)		
Total	10 (32.3%)	21 (67.7%)	31 (100%)		

sion, negative HER2 status, tumor grade, and age at presentation, but not with lymph node status, tumor size, or lymphovascular invasion.[29] Purdie *et al* reported that absent PgR expression was significantly associated with poorer prognosis, even within ER-positive cases.[30] These reports suggests that the assessment of PgR expression in breast carcinomas may still benefit from patient's prognosis. However, it should be noted that most of the treatment response data in previous reports relate to surgical specimens. In this setting, the results of PgR status compared between CNB and surgical specimens in our study may have clinical importance.

Recently, there have been increasing demands to evaluate the use of HER2-targeted agents in neoadjuvant therapy for both primary operable and inoperable HER2-positive breast carcinoma. It is therefore important to achieve a more definitive diagnosis of HER2 status in preoperative CNB. The concordance rate of HER2 status was 64–98.8% by IHC in previous reports (Table 1).[20–33] For HER2 determination, our results showed a relatively low concordance rate of 86.3%. We demonstrated that there was discordance in judgment of HER2 status between CNB specimens and surgically resected specimens in some cases. As breast carcinoma is a heterogeneous disease, we detected the strongest HER2 expression area in these tumors in surgical specimens. Therefore, it assumed that HER2 scores from surgical specimens were higher than those from CNB in these cases taken randomly from breast carcinomas. Our results suggest avoiding completely relying on HER2 status from CNB and marker results should be interpreted cautiously. Moreover, our results provided in conclusive evidence regarding the value of HER2 IHC on CNB, as *in situ* hybridization was not performed on all cases in our report, limiting the interpretation of the staining results. Mann *et al* reported that FISH assays of HER2 overexpression were more sensitive than IHC assays.[20] Therefore, discordance in HER2 expression may be due to differences in methodology because HER2 expression was analyzed by IHC. Further study, including validation of HER2 IHC with fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH), is needed to clarify these results.

There are only a few studies that have reported differences in the Ki-67 index between CNB and surgical specimens with hormone receptors and HER2 status.[30,31] We found high concordance rates in CNB and surgical specimens, which provide reliable information about Ki-67 with invasive carcinoma. However, Ki-67 expression between CNB and surgical specimens in noninvasive carcinoma showed a low concordance rate of 62.5%, with no significance. The major reason for lower Ki-67 expression may be tumor heterogeneity and that CNB may not adequately represent its nature. The limitations of CNB such as a smaller sample size, sampling errors on a heterogeneous tumors and artefacts as in the previous report should be considered in the discrepancy for Ki-67.

In conclusion, this study is the latest to determine the correlation rate for ER, PgR, HER2 status, and Ki-67 index between CNB and surgical specimens. As we found a number of discordant cases in the estimation for which a discrepancy in determination led to a change in treatment, it should be determined based on the final surgical specimen whenever possible. However, our results do not entirely invalidate the use of CNB for assessment if they are

the only source of tumor tissue available, but suggest a more cautious approach in their interpretation when clinical decisions are being made.

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