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Concordance of immunohistochemistry between core needle biopsy and surgical resection of breast cancer

Faruk Erdem KOMBAK[1,*], Hülya ŞAHİN[1], Hande MOLLAMEMİŞOĞLU[1], İdris ÖNEM[1], Handan KAYA[1], Onur BUĞDAYCI[2], Erkin ARIBAL[2]

[1]Department of Pathology, Faculty of Medicine, Marmara University, İstanbul, Turkey
[2]Department of Radiology, Faculty of Medicine, Marmara University, İstanbul, Turkey

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Background/aim: The purpose of this study was to evaluate the concordance of immunohistochemical (IHC) parameters of breast lesions between the core needle biopsy (CNB) and the surgical resection specimen.

Materials and methods: CNB and resection specimens of female patients were retrospectively analyzed. ER, PR, HER-2, and Ki-67 parameters were compared for each patient. A total of 284 cases were assessed. Forty-one and 48 cases were excluded from the HER-2 and Ki-67 examinations, respectively, because the CNBs did not allow for IHC.

Results: Concordance rates were 93.3% for ER, 89.4% for PR, 90.1% for HER-2, and 80.9% for Ki-67.

Conclusion: CNB is accurate for the evaluation of the surrogate molecular profile of invasive breast cancer despite the heterogeneity of tumors.

Key words: Breast cancer, image-guided biopsy, immunohistochemistry, Ki-67, hormone receptors, c-erb-B2

1. Introduction

Core needle biopsy (CNB) is a reliable method that is widely used for preoperative diagnosis of breast cancer and specification of prognostic and predictive parameters (1–3). Neoadjuvant systemic therapy can be organized with the guidance of CNB (2). For cases with complete remission after neoadjuvant systemic therapy, CNB can be the only method that reflects the characteristics of the tumor (4–6). On the other hand, CNB is a useful tool for the diagnosis and management of sentinel lymph node metastasis (7) and distant metastasis (8). In addition to its diagnostic and predictive role in breast cancer, CNB is used to support patients' education, cooperation, and consent (9). In spite of its advantages, CNB may not completely represent the biological profile of the tumor in all cases, resulting from not only methodological limitations but also intratumoral heterogeneity (10).

Numerous studies investigated the disparity between the CNB and resection specimen (RS) results and reported different findings. Diagnosis of breast carcinoma was reported to be concordant in 96% to 100% of cases in a previous study (11). Accuracy of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) status has been found to range from 77.8% to 100% for ER, 69% to 97.1% for PR, and 60% to 98% for HER-2 in the literature (8). For Ki-67, the criteria for subclassification of breast carcinomas are yet to be defined, although a few suggestions of cutoffs have been made. Our purpose in this study is to assess the concordance of immunohistochemical assessment of the surrogate molecular profile of tumors by comparing CNBs and RSs and to clarify the reasons for discrepancies.

2. Materials and methods

2.1. Patients

Among the female patients who were admitted to our hospital with the diagnosis of operable invasive breast cancer between December 2011 and December 2015, the ones with a record of both CNB and RS were assessed retrospectively in this study. Male patients, patients who received neoadjuvant chemotherapy, and patients who had their pathology reviewed only in our hospital were excluded. Characteristics of the largest tumor were taken into account while assessing the cases with more than one tumor focus.

* Correspondence: erdemkombak@hotmail.com

2.2. Immunohistochemistry (IHC)

CNBs or RSs were kept in neutral buffered formalin overnight, providing an optimum fixation time between 6 and 72 h, then embedded in paraffin, as suggested by the ASCO/CAP testing guidelines (3,10,12,13). Immunohistochemical staining was performed on sections of 4 μm with the Bond-Max autoimmunostainer (Leica Biosystems, Nussloch, Germany) by using ER antibody at 1:100 (Clone 6F11 mouse monoclonal antibody, Leica Biosystems, Newcastle, United Kingdom), PR antibody at 1:100 (Clone 16 mouse monoclonal antibody, Leica Biosystems), HER-2 antibody at 1:100 (Clone 10A7 mouse monoclonal antibody, Leica Biosystems), and Ki-67 antibody at 1:100 (Clone K2 mouse monoclonal antibody, Leica Biosystems).

The IHC slides were assessed as part of the daily routine by two pathologists, one of whom was an experienced consultant for breast pathology. The cutoff point for ER and PR positivity was set at 1% (Figures 1 and 2). HER-2 overexpression was scored as 1+ (incomplete membrane staining in any proportion of tumor cells), 2+ (complete membrane staining that was either nonuniform or weak in intensity but with obvious circumferential distribution in at least 10% of tumor cells, or invasive tumors with intense, complete membrane staining of 10% or fewer tumor cells), or 3+ (uniform, intense membrane staining of 10% of invasive tumor cells) in accordance with the ASCO/CAP guidelines (10) (Figures 3 and 4). For Ki-67 assessments, the slides were scanned at low magnification (100×) to identify and encircle the hot-spot (HS); this was defined as the area containing the highest density of Ki-67-labeled tumor cells by visual impression. Tumor cells in consecutive high power fields were counted in HSs. Any nuclear staining regardless of intensity was considered positive and the percentage of positive tumor cells was recorded. A cutoff point of 14% was used, in regards to the 2011 St Gallen International Expert Consensus (14). All results were assessed overall and in separate groups for histologic type, tumor grade, and pathological tumor stage. Groups were as follows: ductal (DC), lobular (LC), and mixed & other (MO) for histologic type; grade 1 (G1), grade 2 (G2), and grade 3 (G3) for tumor grade; and pT1, pT2, pT3, and pT4 for pathological stage.

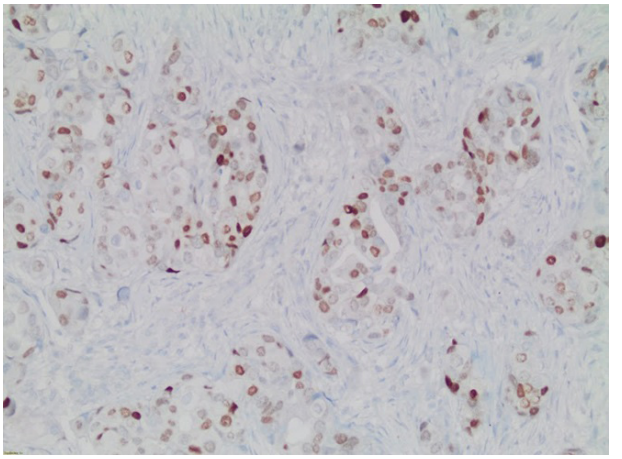

Figure 2. Intratumoral heterogeneity of PR immunoreactivity (400×).

2.3. Statistical analysis

The chi-square test was applied to compare the diagnoses and immunohistochemical findings of ER, PR, HER-2, and Ki-67 stains across paired CNB and RS samples using SPSS 15. $P < 0.05$ was considered statistically significant.

3. Results

Records of 473 patients with RSs were collected. CNB was performed for only 307 (65%) of them. Among those

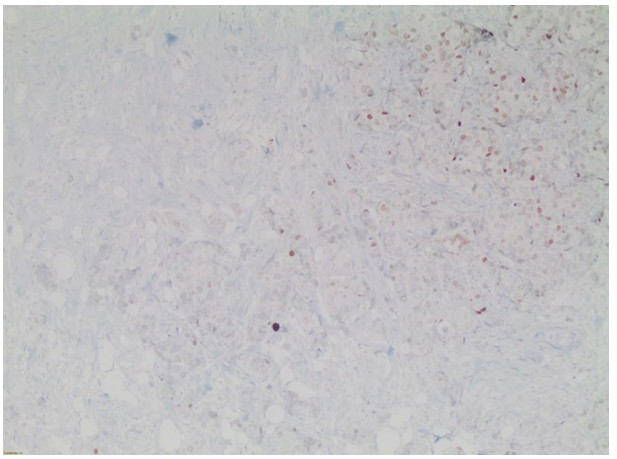

Figure 1. Intratumoral heterogeneity of PR immunoreactivity (100×).

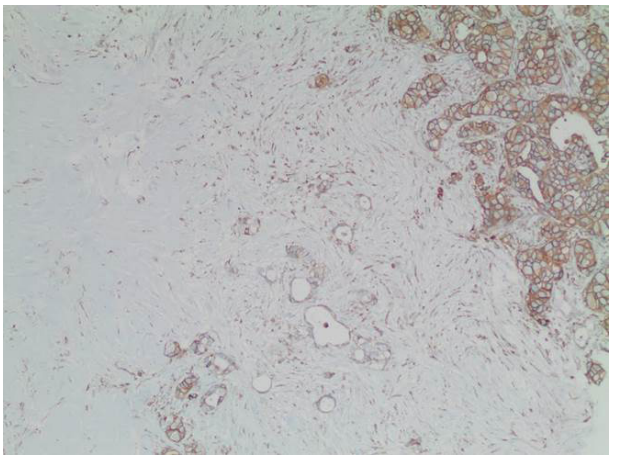

Figure 3. Intratumoral heterogeneity of HER-2 immunoreactivity (100×).

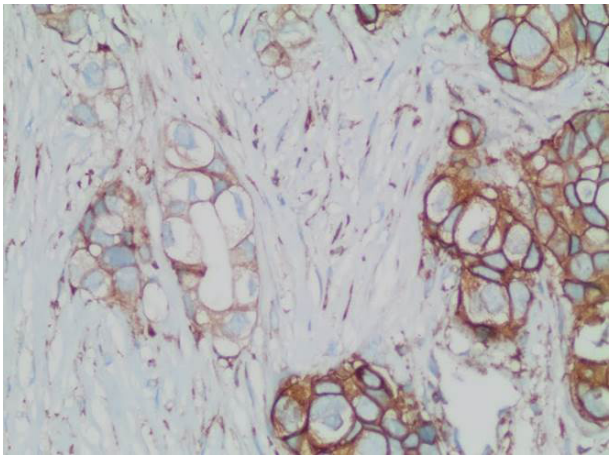

Figure 4. Intratumoral heterogeneity of HER-2 immunoreactivity (400×).

307 cases, 12 were diagnosed as carcinoma in situ, 3 were diagnosed as microinvasive carcinoma, and 8 were diagnosed as benign changes. After excluding them, a total of 284 cases were assessed. Forty-one and 48 cases were excluded from the HER-2 and Ki-67 examinations, respectively, because the CNBs did not allow for IHC.

Mean age was 52.3 with the range of 22–84 years. Tumor characteristics are listed in Table 1. Seven cases diagnosed as ductal carcinoma in CNB were discerned to be lobular carcinoma based on the RS. This subset of discrepancy accounted for 2.5% of all cases. There was no mismatch between benign/in situ/malignant lesions, quite likely due to clinical-radiological-pathological correlation meeting provisions.

Overall ER was positive in 87.3% of CNBs and 82.7% of RSs ($P < 0.001$). There was discrepancy in 19 cases and the concordance was 93.3%. Sixteen of the discrepant cases were ER-positive in CNB and ER-negative in RS. Three cases were ER-negative in CNB and weakly ER-positive in RS. Concordance for separate groups is shown in Table 2.

PR was positive in 80.6% of CNBs; however, it was positive in 75.7% of RSs ($P < 0.01$). The overall concordance was 89.4% with discrepancy in 30 cases. Eight cases that were PR-negative in CNB were PR-positive in RS. On the other hand, 22 discrepant cases were PR-positive in CNB and PR-negative in RS. Concordance for separate groups is shown in Table 2.

HER-2 IHC was found positive in 18.9% of CNBs and 18.5% of RSs ($P < 0.01$). There were 24 discrepant cases, and the overall concordance was 90.1%. Eleven of discrepant cases were HER-2-negative in CNB, although they were HER-2-positive in RS. The other 13 discrepant cases were HER-2-positive in CNB and negative in RS. Concordance for separate groups is shown in Table 2.

The Ki-67 proliferation index was <14% in 36.9% of CNBs, <14% in 34.8% of RSs, ≥14% in 63.1% of CNBs, and ≥14% in 65.2% of RSs. There were a total of 45 discrepant cases, and the overall concordance was 80.9%. Concordance for separate groups is shown in Table 2.

Histologic grade was estimated only for RSs. Thirty (10.6%) cases were grade 1, while 130 (45.8%) and 124

Table 1. Characteristics of tumors included in the study, n (%).

Characteristics of tumors					
		CNB	RS		Number of discordant cases
Histologic subtype	Ductal Lobular Mixed and other	245 (86.3%) 8 (2.8%) 31 (12.5%)	205 (72.2%) 17 (5.9%) 62 (21.8%)		
ER	- +	36 (12.6%) 248 (87.3%)	49 (17.2%) 235 (82.7%)	$P < 0.001$	19
PR	- +	55 (19.3%) 229 (80.6%)	69 (24.3%) 215 (75.7%)	$P < 0.001$	30
Her-2	0 1 2 3	159 (65.4%) 16 (6.6%) 22 (9%) 46 (18.9%)	169 (69.5%) 14 (5.8%) 15 (6.2%) 45 (18.5%)	$P < 0.001$	24
Ki-67	<14 % ≥14 %	87 (36.9%) 149 (63.1%)	82 (34.8%) 154 (65.2%)	$P < 0.001$	45

Table 2. Concordance of IHC parameters within subgroups, n (%).

	ER con.	PR con.	HER-2 con.	Ki-67 con.
DC	195 (95.1%)	183 (89.3%)	155 (87.6%)	141 (81%)
LC	17 (100%)	17 (100%)	15 (93.8%)	10 (62.5%)
MO	53 (85.5%)	52 (83.9%)	49 (96.1%)	40 (85.1%)
G1	28 (93.3%)	28 (93.3%)	23 (92%)	18 (82%)
G2	124 (95.4%)	121 (93.1%)	96 (88.9%)	82 (75.6%)
G3	111 (89.5%)	105 (84.7%)	99 (90%)	92 (86%)
pT1	102 (96.2%)	103 (97.2%)	81 (92%)	68 (80%)
pT2	148 (91.9%)	142 (88.2%)	127 (89.4%)	115 (83.3%)
pT3	11 (91.7%)	11 (91.7%)	9 (83.3%)	7 (66.7%)
pT4	5 (100%)	5 (100%)	2 (50%)	2 (50%)

con.: Concordance, DC: ductal carcinoma, LC: lobular carcinoma, MO: mixed and other, G: grade, pT: pathologic stage of tumor.

(43.7%) cases were grade 2 and 3, respectively. In this study, we noted pT and pN statuses as markers of tumor size and regional lymph node involvement, as summarized in Table 3.

4. Discussion

As breast cancer is the most frequently diagnosed cancer and the second most frequent cause of cancer-related death in women, preoperative assessments of diagnosis and of prognostic factors are becoming more and more important steps in the management of patients. CNB is a routinely used method for preoperative assessment of breast cancer patients (1–3,5). CNB may not completely represent the biological profile of the tumor in all cases because of sampling errors (15), insufficient sample size of the CNB, fixation problems of RSs, intratumoral heterogeneity, and menopausal status of patients (3,5,8,9). The aim of this study was to assess the concordance of CNB and RS results and to clarify the reasons for discrepancies.

Table 3. Tumor size and regional lymph node involvement, n (%).

pT	1	106 (37.3%)
	2	161 (56.7%)
	3	12 (4.2%)
	4	5 (1.8%)
pN	X 0 1 2 3	9 (3.2%) 154 (54.2%) 83 (29.2%) 24 (8.5%) 14 (4.9%)

Concordance rates between CNB and RS were found as 93.3%, 89.4%, 90.1%, and 80.9% for ER, PR, HER-2, and Ki-67, respectively, in this study. In our multidisciplinary algorithm, cases lacking clinical-radiological-pathological correlation are considered "sampling errors" and submitted to repeat biopsies, which resulted in a lack of mismatch for benign/in situ/malignant diagnoses between CNBs and RSs. In the literature, concordance rates of ER, PR, and HER-2 have been found to range between 77.8% and 100% for ER, 69% and 97.1% for PR, and 60% and 98% for HER-2 (6,8). We noted a higher concordance rate for ER than PR, a pattern that has been described in the literature (1,5). Concordance rates of ER for separate groups were close. PR concordance is highest in the LC, G2, and pT4 groups. PR concordance was seemingly close in separate groups. Cases with ER/PR/HER-2-positive tumors in the CNB may not be restained upon RS (16), since a negative result in RS would only change the estimated effectivity of the given neoadjuvant and/or adjuvant therapy (17–20). On the other hand, our own experience is that cases with ER/PR/HER-2-negative tumors in CNB must be restained upon RS, especially in the case of contrast between CNB and RS regarding histologic grade, growth pattern, and concomitant inflammatory infiltration.

As tumor size scaled up, Ki-67 concordance tended to decrease, whereas the histologic type and tumor grade were not different at all. The concordance of the Ki-67 proliferation index is controversial (21,22), since it is easily affected by many factors such as surgical time interval (23), cold ischemic time (24), prior biopsy size, heterogeneity of histologic grade (25) fixation time despite controversies (26), and interobserver variation. After the suggestion of Ki-67 as a predictive marker

for adjuvant chemotherapy, interobserver variation and methodological issues have been increasingly discussed (27,28). Some recommendations for Ki-67 assessment were presented in 2011 and the lack of systematic comparisons of Ki-67 expression levels between tissue microarrays and whole sections was noted (27). As an example, the Ki-67 cutoff point of 14%, recommended for treatment decisions by the St Gallen 2011 guidelines, was based on data from a series of tissue microarrays combined with gene expression analysis (29). However, the clinical implications of these findings have not been well documented. In this study, we found a slight difference in proliferation with median Ki-67 positivity of 15% for CNBs and 20% for RSs. However, there were a total of 55 discordant cases, which is rather high compared to the discordance rates for ER/PR and HER-2.

We investigated the concordance of diagnostic and prognostic parameters between CNBs and RSs in 284 breast cancer patients' paired samples, which is one of the largest series published so far on the subject. Although concordance rates of ER, PR, HER-2, and Ki-67 statuses were high in this study, similar to the published literature, notable differences between CNB and RS were found (30). These differences were found to be primarily due to intratumoral heterogeneity.

In conclusion, our study indicates that CNB is accurate for the evaluation of predictive and prognostic immunohistochemical markers of invasive breast cancer despite the heterogeneity of tumors. The immunohistochemical evaluation of these markers does not need to be repeated on RS, unless there is negativity in CNB or the biopsy is inadequate. Repeat tests are needed on RSs in such cases to prevent patients from missing the chance of potential targeted therapy.

References

1. Lorgis V, Algros MP, Villanueva C, Chaigneau L, Thierry-Vuillemin A, Nguyen T, Demarchi M, Bazan F, Sautiere JL, Maisonnette-Lescot Y et al. Discordance in early breast cancer for tumour grade, estrogen receptor, progesteron receptors and human epidermal receptor-2 status between core needle biopsy and surgical excisional primary tumour. Breast 2011; 20: 284-287.
2. O'Leary R, Hawkins K, Beazley JC, Lansdown MR, Hanby AM. Agreement between preoperative core needle biopsy and postoperative invasive breast cancer histopathology is not dependent on the amount of clinical material obtained. J Clin Pathol 2004; 57: 193-195.
3. Asogan AB, Hong GS, Arni Prabhakaran SK. Concordance between core needle biopsy and surgical specimen for ER, PgR and Her2neu receptor status in breast cancer and study of difference in reliability between the two groups with the change in ASCO/CAP guidelines. Singapore Med J 2017; 58: 145-149.
4. Burge CN, Chang HR, Apple SK. Do the histologic features and results of breast cancer biomarker studies differ between core biopsy and surgical excision specimens? Breast 2006; 15: 167-172.
5. Arnedos M, Nerurkar A, Osin P, A'Hern R, Smith IE, Dowsett M. Discordance between core needle biopsy (CNB) and excisional biopsy (EB) for estrogen receptor (ER), progesterone receptor (PgR) and HER2 status in early breast cancer (EBC). Ann Oncol 2009; 20: 1948-1952.
6. Park SY, Kim KS, Lee TG, Park SS, Kim SM, Han W, Noh DY, Kim SW. The accuracy of preoperative core biopsy in determining histologic grade, hormone receptors, and human epidermal growth factor receptor 2 status in invasive breast cancer. Am J Surg 2009; 197: 266-269.
7. Giuliani M, Patrolecco F, Rella R, Di Giovanni SE, Infante A, Rinaldi P, Romani M, Mule A, Arciuolo D, Belli P et al. Can breast cancer biopsy influence sentinel lymph node status? Clin Breast Cancer 2016; 16: e153-e157.
8. Nakamura R, Yamamoto N, Shiina N, Miyaki T, Ikebe D, Itami M, Shida T, Miyazaki M. Impact of host and histopathological factors on the discrepancies in estrogen receptor, and progesterone receptor, and HER2 status between core needle biopsy and surgically excised tumors. Breast 2016; 26: 141-147.
9. Cahill RA, Walsh D, Landers RJ, Watson RG. Preoperative profiling of symptomatic breast cancer by diagnostic core biopsy. Ann Surg Oncol 2006; 13: 45-51.
10. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013; 31: 3997-4013.
11. Verkooijen HM; Core Biopsy After Radiological Localisation (COBRA) Study Group. Diagnostic accuracy of stereotactic large-core needle biopsy for nonpalpable breast disease: results of a multicenter prospective study with 95% surgical confirmation. Int J Cancer 2002; 99: 853-859.
12. Lim TH, Lim AS, Thike AA, Tien SL, Tan PH. Implications of the updated 2013 American Society of Clinical Oncology/College of American Pathologists guideline recommendations on human epidermal growth factor receptor 2 gene testing using immunohistochemistry and fluorescence in situ hybridization for breast cancer. Arch Pathol Lab Med 2016; 140: 140-147.
13. Overcast WB, Zhang J, Zynger DL, Tozbikian GH. Impact of the 2013 ASCO/CAP HER2 revised guidelines on HER2 results in breast core biopsies with invasive breast carcinoma: a retrospective study. Virchows Arch 2016; 469: 203-212.

14. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ; Panel Members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011; 22: 1736-1747.

15. Hukkinen K, Kivisaari L, Heikkila PS, Von Smitten K, Leidenius M. Unsuccessful preoperative biopsies, fine needle aspiration cytology or core needle biopsy, lead to increased costs in the diagnostic workup in breast cancer. Acta Oncol 2008; 47: 1037-1045.

16. Rakha EA, Pigera M, Shin SJ, D'Alfonso T, Ellis IO, Lee AH. Human epidermal growth factor receptor 2 testing in invasive breast cancer: should histological grade, type and oestrogen receptor status influence the decision to repeat testing? Histopathology 2016; 69: 20-24.

17. Dekker TJ, Smit VT, Hooijer GK, Van de Vijver MJ, Mesker WE, Tollenaar RA, Nortier JW, Kroep JR. Reliability of core needle biopsy for determining ER and HER2 status in breast cancer. Ann Oncol 2013; 24: 931-937.

18. Wojnar A, Bartosz Pula B, Podhorska-Okolow M, Dziegiel P. Discrepancies between HER2 assessment from core needle biopsies and surgical specimens of invasive ductal breast carcinoma. Adv Clin Exp Med 2013; 22: 27-31.

19. Wuerstlein R, Sotlar K, Gluz O, Otremba B, von Schumann R, Witzel I, Schindlbeck C, Janni W, Schem C, Bauerfeind I et al. The West German Study Group Breast Cancer Intrinsic Subtype study: a prospective multicenter decision impact study utilizing the Prosigna assay for adjuvant treatment decision-making in estrogen-receptor-positive, HER2-negative early-stage breast cancer. Curr Med Res Opin 2016; 32: 1217-1224.

20. Zardavas D, Irrthum A, Swanton C, Piccart M. Clinical management of breast cancer heterogeneity. Nat Rev Clin Oncol 2015; 12: 381-394.

21. Knutsvik G, Stefansson IM, Aziz S, Arnes J, Eide J, Collett K, Akslen LA. Evaluation of Ki67 expression across distinct categories of breast cancer specimens: a population-based study of matched surgical specimens, core needle biopsies and tissue microarrays. PLoS One 2014; 9: e112-121.

22. Romero Q, Bendahl PO, Klintman M, Loman N, Ingvar C, Ryden L, Rose C, Grabau D, Borgquist S. Ki67 proliferation in core biopsies versus surgical samples - a model for neo-adjuvant breast cancer studies. BMC Cancer 2011; 11: 341.

23. Chen X, Zhu S, Fei X, Garfield DH, Wu J, Huang O, Li Y, Zhu L, He J, Chen W et al. Surgery time interval and molecular subtype may influence Ki67 change after core needle biopsy in breast cancer patients. BMC Cancer 2015; 15: 822.

24. Neumeister VM, Anagnostou V, Siddiqui S, England AM, Zarrella ER, Vassilakopoulou M, Parisi F, Kluger Y, Hicks DG, Rimm DL. Quantitative assessment of effect of preanalytic cold ischemic time on protein expression in breast cancer tissues. J Natl Cancer Inst 2012; 104: 1815-1824.

25. Focke CM, Decker T, van Diest PJ. Reliability of histological grade in breast cancer core needle biopsies depends on biopsy size: a comparative study with subsequent surgical excisions. Histopathology 2016; 69: 1047-1054.

26. Kalkman S, Bulte JP, Halilovic A, Bult P, van Diest PJ. Brief fixation does not hamper the reliability of Ki67 analysis in breast cancer core-needle biopsies: a double-centre study. Histopathology 2015; 66: 380-387.

27. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011; 103: 1656-1664.

28. Polley MY, Leung SC, McShane LM, Gao D, Hugh JC, Mastropasqua MG, Viale G, Zabaglo LA, Penault-Llorca F, Bartlett JM et al. An international Ki67 reproducibility study. J Natl Cancer Inst 2013; 105: 1897-1906.

29. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst 2009; 101: 736-750.

30. Prendeville S, Feeley L, Bennett MW, O'Connell F, Browne TJ. Reflex repeat HER2 testing of grade 3 breast carcinoma at excision using immunohistochemistry and in situ analysis: frequency of HER2 discordance and utility of core needle biopsy parameters to refine case selection. Am J Clin Pathol 2016; 145: 75-80.