ORIGINAL ARTICLE

Comparison of Immunohistochemical Markers in Core Needle Biopsy and Excisional Biopsy in Breast Carcinoma

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ABSTRAK

Reseptor estrogen (ER), reseptor progesterone (PR) dan reseptor faktor ketumbuhan epidermal manusia 2 (HER2) immunohistokimia adalah penanda penting dan berperanan di dalam pengurusan pesakit yang menghidap neoplastik payudara. Di dalam kajian ini, kami membandingkan kadar konkordan ER, PR, dan HER2 diantara biopsi jarum teras dan biopsi eksais pada tisu neoplastik payudara melibatkan pesakit pesakit Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) yang di diagnosa diantara bulan Januari 2002 sehingga Disember 2012. Seramai 93 pesakit wanita yang menjalani biopsi jarum teras dan kemudiannya biopsi eksais termasuk di dalam kajian retrospektif ini. Kajian immunohistokimia telah digunakan untuk menentukan pewarnaan ER, PR dan HER2. Pewarnaan ER dan PR telah dianalisa menggunakan skor Allred (0 hingga 8) manakala analisa pewarnaan HER2 menggunakan sistem skor 0 hingga 3+. Skor keputusan dibanding antara kedua biopsy tersebut untuk menentukan kadar konkordan. Sebanyak 93 sampel berjaya dibandingkan diantara kedua biopsi tersebut untuk pewarnaan immunohistokimia ER dan PR. Kadar konkordan ER adalah sebanyak 80 kes (86%) dan 13 kes (14%) bagi yang tidak konkordan. Kadar konkordan PR adalah sebanyak 82 kes (88.2%) dan 11 kes (11.8%) bagi yang tidak konkordan. Sebanyak 87 sampel telah dibandingkan untuk kajian pewarnaan immunohistokima HER2 dan kadar konkordan adalah sebanyak 62 kes (71.3%) dan 25 kes (28.7%) bagi yang tidak konkordan. Di dalam kajian ini, kadar konkordan diantara biopsi tisu jarum teras dan biopsi eksais bagi ER dan PR adalah tinggi. Manakala, kadar konkordan untuk pewarnaan HER2 adalah kurang konsisten. Kesimpulannya, analisa immunohistokimia untuk biopsi tisu jarum teras dapat meramal keputusan penanda pada tisu biopsy eksais di dalam penyakit neoplastik payudara.

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Kata kunci: neoplastik payudara, biopsi tisu jarum teras, reseptor estrogen, reseptor progesterone, HER2

ABSTRACT

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) immunohistochemistry are important markers in the management of patient with breast carcinoma. In this study, we determine the concordance rate of ER, PR and HER2 immunohistochemistry markers between core needle biopsy (CNB) and excisional biopsy (EB) of breast carcinoma in patients of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from January 2002 until December 2012. A total of 93 female patients with CNB and subsequent EB were included in this retrospective descriptive study. Immunohistochemistry is used to determine ER, PR and HER2. ER and PR was graded using Allred score (0 to 8) while HER2 was scored from 0 to 3+. The markers between these two biopsies were compared to determine the concordance rate. In ER and PR, 93 samples were compared. ER was concordant in 80 cases (86.0%) and 13 cases (14.0%) was discordant. PR was concordant in 82 cases (88.2%) and discordant in 11 cases (11.8%). In HER2, 87 samples were compared and 62 cases (71.3%) were concordant while 25 cases (28.7%) were discordant. Concordance between CNB and EB was high for ER and PR. However, concordance rate for HER2 immunohistochemistry was less consistent. Overall, immunohistochemical analyses of CNB reflect the tumour marker status of the excised specimen.

Keywords: breast carcinoma, core needle biopsy, estrogen receptor, progesterone receptor, HER2

INTRODUCTION

Core needle biopsy (CNB) is widely used in routine preoperative practice as part of the triple assessment in patients with suspected breast carcinoma (Li et al. 2012; Wai et al. 2013). Studies have reported good concordance rate of 91%-100% between CNB and excisional biopsy (EB) for diagnosis of breast carcinoma with a specificity rate ranging from 96% to 100% (Li et al. 2012).

Immunohistochemical hormonal receptor (HR) markers such as estrogen receptor (ER), progesterone receptor (PR) and HER2 performed on tumor samples from CNB has been used as biologic markers in breast cancers for predicting response to specific therapeutic agents. Similarly, HER2 over expression has been associated with worse prognosis in newly diagnosed patients with breast carcinoma, and is a determinant of response to trastuzumab (Arnedos et al. 2009). However, challenges may arise as analysing HR markers on CNB containing small tissue samples may not accurately reflect the overall biologic profile of the heterogenous tumour. Thus, HR markers on CNB may lead to false negative or positive results. When "false negative" HR test

results are found, these deprive women of the proven benefits of endocrine therapies and may lead to choosing unnecessary chemotherapy treatments with significant financial costs and toxicities (Uy et al. 2010).

In the light of false negative or false positive HR markers that may be found on CNB, the main aim of the present study was to compare the status of ER, PR and HER2 markers performed on CNB with the immunohistochemical results in the subsequent mastectomy/ wide local excision/lumpectomy (EB) for patients diagnosed with breast cancer. More specifically, this study aimed to determine the level of concordance between hormonal status identified on CNB and EB performed in one of the local teaching hospitals in Malaysia.

MATERIALS AND METHODS

PATIENTS AND SAMPLES

A retrospective cohort reviewing data and medical records of patients diagnosed with breast carcinoma from January 2002 until December 2012 in UKMMC was performed. The study was approved by the UKM Medical Centre Ethics Committee/ Institutional Review Board (UKM Ethics Committee Reference No: UKM 1.5.3.5/244/FF-077-2013). A total of 107 female patients with CNB and subsequent EB diagnosed with primary breast carcinoma were included in this descriptive study. Patients who had local recurrent or non-primary carcinoma were totally excluded from this study. Patients who had received neoadjuvant radio or chemotherapy or hormonal treatment between CNB and the final excised specimens were also excluded from this study.

ER, PR AND HER2 DETERMINATION

Immunohistochemistry was used to determine ER, PR and HER2 hormonal status. ER and PR were graded using Allred score from 0 to 8 and scores of more than 2 were considered positive. HER2 was scored from 0 to 3+. Scoring of 2+ and 3+ in HER2 status analysis were taken as positive while 0 and 1+ was considered negative. The final results between CNB and EB were compared to determine the concordance and discordance rate.

STATISTICAL ANALYSIS

The concordance rate, sensitivity, specificity, positive and negative predictive value were compared using SPSS version 19 by considering CNB as test assessment and EB as the gold standard.

RESULTS

CONCORDANCE RATE

A total of 93 samples were included in this study. A total of 76 patients from the 93 samples analysed, had infiltrating ductal carcinoma, diagnosed both on CNB and EB (81% respectively).

In CNB, PR was scored as positive in 65 (70%) and negative in 28 (30%) of the cases. In the EB, PR was positive in 62 (67%) of the cases and negative in 31 (33%). Discordance of PR status between CNB and EB was seen in 11 cases (11.8%).

ER status was 53% positive on CNB compared to 48% in the excised specimen. Only 12 samples were discordant (14%). 8 of the 12 discordant samples showed ER positivity on CNB but negative on EB. The remaining four discordant samples were ER negative on CNB but positive on EB.

Only 87 samples were available for HER2 status assessment. Fourty nine (56.3%) samples showed HER2 positivity on CNB and 38 (43.7%) samples were negative for HER2. In the EB, 39 samples were HER2 positive (44.8%) and 48 were negative (55.2%). A total of 26 samples were discordant with a discordant rate of 28.7%. Eighteen of these discordant samples showed HER2 positivity on CNB but were negative on EB. Summarized results of these findings were shown in Table 1.

SENSITIVITY AND SPECIFICITY OF CNB AND EB IN DETECTING ER, PR AND HER2 STATUS IN BREAST CARCINOMA

CNB was as sensitive as EB in determining ER and PR status. However, the sensitivity in determining HER2 on CNB was less consistent. The rates of sensitivity, specificity, positive and negative predictive values were summarized in Table 2 with EB as the reference for each marker.

DISCUSSION

In routine preoperative practice in UKMMC, CNB is often used as part of a triple assessment in patients with suspected breast carcinoma. The expression of these markers will guide the Clinician in the

Table 1: Concordance between CNB and EB for ER, PR and HER2 results

CNB	EB		Total	Concordance rate (%)	p value
	Positive	Negative			
ER					
Positive	41	8	49	86	1
Negative	4	40	44		
Total	45	48	93		
	K=0.84				
PR					
Positive	58	7	65	88.2	1
Negative	4	24	28		
Total	62	31	93		
	K=0.89				
HER2					
Positive	31	18	49	71.3	0.9
Negative	8	30	38		
Total	39	48	87		
	K=0.70				

$p<0.05$ =significant

K= kappa value

Table 2: Sensitivity, specificity, positive and negative predictive value for CNB compared with EB

Rate	ER (%)	95%CI	PR (%)	95%CI	HER2 (%)	95% CI
Sensitivity	91.1	0.852-0.968	93.5	0.8849-0.9851	79.4	0.6329-0.9551
Specificity	83.3	0.754-1.584	77.4	0.6890-0.8590	62.5	0.5199-0.7301
Positive predictive value	83.7	0.765-1.605	89.2	0.8289-0.9551	63.3	0.5246-0.7414
Negative predictive value	90.9	0.852-1.762	85.7	0.7859-0.9281	78.9	0.6292-0.9488

therapeutic management of the patient. Previous studies concluded that immunohistochemical results from CNB tend to be less reliable than those analysed on excised specimens as CNB represent limited sample of tissue with possible tumour heterogeneity (Burge et al. 2006; Arnould et al. 2012).

CNB and EB samples from patients assessed in this study was not subjected to any mode of preoperative treatment, as treatment have been known to alter the tumour biologic marker such as ER, PR and HER2 (Honkoop et al. 1997). However, the tumour marker alterations seen in treated specimens may not be consistent with HER2. More recently, HER2 status was shown to remain unchanged when preneoadjuvant and post neoadjuvant specimens are compared (D'Alfonso et al. 2010).

Previous studies found concordance rates for CNB and surgically excised specimens range between 81.3% to 100% for ER, between 42% to 89% for PR and from 86.9% to 100% for HER2 (Burge et al. 2006; Sutela et al. 2008; Wood et al. 2007; Tamaki et al. 2010). In agreement with previous findings (Burge et al. 2006; Wood et al. 2007; Sutela et al. 2008; Ricci et al. 2012), the present study found good concordance between CNB and EB for ER and PR. Previous reports have also found that the concordance rate between CNB and EB for ER was higher than PR (Arnedos et al. 2009). However, in the present study, concordance rate between CNB and EB for PR was slightly higher than that seen for ER, possibly due to better fixation in the CNB specimen.

In the present study, discordance between CNB and EB for ER was 14% and this finding is consistent with a previous study (Connor et al. 2002). False negativity for ER was seen in four cases, indicating that all ER negative results on CNB should be further confirmed with EB. As previously highlighted by Connor et al. (2002), false positivity for ER observed in eight cases of this study suggest sampling error within the tumour periphery and possibly poor fixation in the excised specimen.

While comparing previous studies (Wood et al. 2007; Tamaki et al. 2010; Ricci et al. 2012), the concordance rate between CNB and EB for HER2 in this study was lower than that seen for ER and PR and with a much lower sensitivity and specificity rates. The less consistent concordance rate for HER2 was possibly due to limited number of samples analysed in this study as well as intratumour heterogeneity. Given the limitation of tumour diversity, the concordance rates appear to be

dependent on the number of cores analysed in that the higher number of cores are analysed, the more concordant are the tumour markers between EB and CNB (Tamaki et al. 2010).

Although, good concordance rates between CNB and ER were found in the present study, all of these findings were not found to be significant, possibly due to several limitations that may have potentially resulted such as limited number of sampling. In addition, differences in immunohistochemistry assays and fixative procedure may have also influenced the findings of this study. Breast cancers with HER2 2+ on immunohistochemistry are considered equivocal and therefore should undergo fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) methods for confirmation (Arnould et al. 2012). However, in the present study, FISH/CISH status of HER2 2+ cases were not directly accessible due to time constraint and so were considered as positive for ease of analysis. The assumption of HER2 2+ cases as truly positive may have caused selection bias in this study and possibly the high discordant rates seen in HER2.

CONCLUSION

In conclusion, ER and PR immunohistochemistry performed on CNB produce results which accurately reflect those assessed on EB. The concordance rate for HER2 was less consistent, suggesting intratumoural heterogeneity among contributing factors. Concurrent analysis of HER2 with FISH/CISH on breast cancers is required for HER2 2+ cases given the high discordant rates between EB and CNB.

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