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ANATOMICAL PATHOLOGY

Predicting discordant HER2 results in ipsilateral synchronous invasive breast carcinomas: experience from a single institution

SHAUN CHOU[1], TAYYABA KHAN[1], HEMA MAHAJAN[1] AND NIRMALA PATHMANATHAN[1,2]

[1]Department of Tissue Pathology and Diagnostic Oncology, ICPMR, Westmead Hospital, and [2]Westmead Breast Cancer Institute, Westmead, NSW, Australia

Summary

With the emergence of multiple lines of highly effective Human Epidermal Growth Factor Receptor 2 (HER2) directed therapy, accurate identification of HER2 positive tumour has become a critical aspect in the histopathological analysis of breast cancers. Multifocal invasive breast carcinomas are relatively common, and given the aggressive inherent biology of HER2 positive disease, identification of even small tumours with HER2 positive status may be of importance for treatment planning. There are currently no clear guidelines as to whether all of these foci should be tested for HER2 status. We reviewed the results of 172 patients in whom HER2 *in situ* hybridisation (ISH) testing was performed on at least two ipsilateral synchronous invasive carcinomas. Discordant results in different invasive foci were relatively uncommon and occurred in only eight (5%) of the 172 patients. This showed a statistically significant correlation with similarly discordant oestrogen receptor (ER) results. In addition HER2 discordance was more likely amongst different tumour foci if these arose in distinct and separate areas of DCIS. An algorithm based on a combination of College of American Pathologists (CAP) recommendation for HER2 testing, differing ER status and background DCIS profile may be useful in detecting these discordant cases.

Key words: Breast cancer, breast neoplasms, erbB-2, HER2, hormone receptors, *in situ* hybridisation, multicentric, multifocal.

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INTRODUCTION

Ipsilateral multifocal or multicentric invasive breast carcinomas are common.[1] However, it is unusual for multifocal and multicentric carcinomas to have a different oestrogen receptor (ER) or HER2 profile.[2–5] While different ER or HER2 status may have an impact on adjuvant systemic treatment offered to patients, it is not necessarily feasible or cost effective to test every tumour, particularly considering the cost of HER2 *in situ* hybridisation (ISH) testing. This is more relevant in Australia, where ISH testing is used as a first line testing modality for patients with early breast cancer, since they would qualify for government subsidised anti-HER2 therapy through the pharmaceutical benefits scheme only on the basis of a positive HER2 ISH result. The purpose of this study is to determine if there are features that may be predictive of increased likelihood of discordant HER2 results in ipsilateral synchronous invasive breast carcinomas. In addition, we seek to examine the validity of the current College of American Pathologists (CAP) recommendation for HER2 testing in multifocal cancers, where it is recommended that testing is performed on the largest tumour unless the smaller tumours have higher grade or different histology.[6]

MATERIALS AND METHODS

The study was conducted with the approval of the Western Sydney Local Health District Human Research Ethics committee.

A database search was performed in the department of Tissue Pathology and Diagnostic Oncology in Westmead Hospital for patients with multiple ipsilateral invasive breast carcinomas in excision specimens. This covered a period of about 6 years (2008–2014) when HER2 silver *in situ* hybridisation (SISH) testing became routine. All patients who had ER, progesterone receptor (PR) and HER2 SISH testing on at least two invasive carcinomas were included in the study. The patients whose full pathology reports could not be accessed were excluded from the study. Information regarding the included cases was obtained from the pathology reports, and details recorded on every tumour included whether the tumour was invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC), tumour grade, ER and PR immunohistochemistry (IHC) results and HER2 SISH status. In terms of the tumour type, tubulolobular carcinomas were grouped with the lobular carcinomas,[7] whereas those diagnosed as mixed ductal and lobular carcinomas were grouped with the ductal type. Also recorded was whether the invasive carcinomas arose within the same or separate areas of ductal carcinoma *in situ* (DCIS) if at least two of the invasive carcinomas were of the ductal type.

Invasive carcinomas were considered to be separate primary lesions if they formed discrete mass lesions macroscopically. In more complex cases such as those with microscopic invasive carcinomas or macroscopically more ill-defined lesions, the decision as to whether the lesions were designated as separate or part of the same lesion was at the discretion of the reporting pathologists. The decision would be based on a range of factors such as relative location and morphology of the tumour cells. Foci of DCIS were considered separate if they were proven to be separated by a distance of at least 5 mm.

For HER2 ISH testing, the single silver probe (Inform HER2 SISH; Ventana Medical Systems, USA) was used in cases up to June 2012, and additional chromosome enumeration probe 17 (CEP17) on a separate section was performed if required. After June 2012, Inform HER2 dual SISH (Ventana Medical Systems) was used. Reporting of ER, PR and HER2 ISH was based on the guideline provided by the American Society and Clinical Pathology (ASCO).[8–10] Specific comments regarding intra-tumoral HER2 heterogeneity in any of the cases satisfying the inclusion criteria were documented if present.

Chi square tests were performed to determine statistical correlation between concordant and discordant HER2 SISH results versus concordant or discordant tumour type, tumour grade, ER, PR results as well as if the invasive ductal carcinomas arose within the same area of DCIS. Statistical significance was calculated based on the Fisher's exact test and was considered significant if the p value was <0.05.

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Table 1 Patients divided into groups based on concordant/discordant HER2 result versus other features

	Concordant HER2	Discordant HER2	Fisher's exact test
Concordant tumour type	145	8	$p = 0.600$
Discordant tumour type	19	0	
Concordant grade	116	4	$p = 0.246$
Discordant grade	48	4	
Concordant ER	160	6	$p = 0.026$
Discordant ER	4	2	
Concordant PR	141	6	$p = 0.328$
Discordant PR	23	2	
Within same DCIS	54	2	$p = 0.034$
In separate areas of DCIS	96	6	

DCIS, ductal carcinoma *in situ*; ER, oestrogen receptor; PR, progesterone receptor.

In addition, we sought to examine the validity of the current CAP recommendation for HER2 testing in multifocal cancers, where it is recommended that testing is performed on the largest tumour unless the smaller tumours have higher grade or different histology.[6]

RESULTS

A total of 172 patients satisfied the study inclusion criteria. Of these, 157 patients (91%) had two tumours that had receptor and HER2 testing while 15 patients (9%) had testing on three tumours.

Nineteen patients (11%) had different tumour types (i.e., at least 1 IDC and 1 ILC), while 52 patients (30%) had different tumour grades in at least two tumours.

Discordant results were obtained in eight patients (5%) with regard to HER2, seven patients (4%) with regard to ER and 25 patients (15%) with regard to PR. Of these, only two patients (1%) had discordant results in their tumours for both ER and HER2. Of the 158 patients who had at least two invasive ductal carcinomas, 56 (35%) of them arose within the same area of DCIS, whereas the remaining 102 (65%) did not (Table 1)

When the tumours were subdivided into groups based on concordant or discordant HER2 results and tumour types, none of the eight patients with discordant HER2 results had different tumour types, and 19 of 164 patients with concordant HER2 results had different tumour types ($p = 0.600$).

When the tumours were subdivided into groups based on HER2 results and tumour grade, four of the eight patients with discordant HER2 results had discordant tumour grade, while 48 of 164 patients with concordant HER2 results had different tumour grade ($p = 0.246$).

When the tumours were subdivided into groups based on HER2 and ER results, two of the eight patients with discordant HER2 results had discordant ER results, while only four of 164 patients with concordant HER2 results had discordant ER results ($p = 0.026$).

When the tumours were subdivided into groups based on HER2 and PR results, two of the eight patients with discordant HER2 results had discordant PR results, while 23 of 164 patients with concordant HER2 results had discordant PR results ($p = 0.328$).

When the invasive ductal carcinomas were subdivided based on HER2 results and whether they arose in different areas of DCIS, six of the eight patients with discordant HER2 results had invasive carcinomas arising in different areas of DCIS, while 96 of 150 patients with concordant HER2 results had tumours arising in different areas of DCIS ($p = 0.034$).

For the eight patients with discordant HER2 results, HER2 amplification was seen only in the smaller tumour in three patients (Table 2). If the CAP algorithm for tumour selection and testing was strictly adopted, then the HER2 amplified tumour would have been missed in two patients (25%). One

Table 2 Patients with discordant HER2 results

Patient	Size (mm)	Tumour type	Grade	ER	PR	HER2	HER2:CEP17 (ratio)	Within same DCIS
1	30	Micropapillary	3	+	+	+	18 : 2.5 (7.20)	No
	25	NST type	3	+	+	−	3 : 2.9 (1.03)	
2	20	NST type	2	−	−	−	2.95 : 2.5 (1.18)	No
	8	NST type	2	+	−	+	12 : 2 (6.00)	
3	25	NST type	2	+	+	+	5 : 1.8 (2.78)	Yes
	15	NST type	2	+	+	−	1.2 : 2.1 (0.57)	
	10	NST type	2	+	+	−	2.2 : 2.3 (0.96)	
4	16	NST type	1	+	+	−	1.7 : 1.6 (1.06)	No
	8	NST type	3	−	+	+	18 : 2.5 (7.20)	
5	20	NST type	3	+	+	+	>25 : 3.5 (>7.14)	No
	9	NST type	1	+	−	−	1.8 : 1.8 (1.00)	
6	20	NST type	3	+	+	−	1.75 (single probe)	No
	19	NST type	2	+	+	+	6.5 (single probe)	
7	35	NST type	2	+	+	+	8 (single probe)	Yes
	25	NST type	3	+	+	–	3 (single probe)	
	8	NST type	3	+	−	+	8 (single probe)	
8	25	NST type	3	+	−	+	8.5 : 2.2 (3.9)	No
	15	NST type	3	+	−	−	4.25 : 3.5 (1.7)	

The numbers given for Cases 6 and 7 in the 2nd last column indicate the average HER2 copy number in the corresponding tumours obtained from single SISH probe. CEP17 count or HER2:CEP17 ratio was not performed in the tumours for these two patients.

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