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ORIGINAL ARTICLE

Use of tissue microarray for interlaboratory validation of HER2 immunocytochemical and FISH testing

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Aims: To evaluate the use of tissue microarray (TMA) technology as a validation tool for HER2 testing by both immunocytochemistry (ICC) and fluorescence in situ hybridisation (FISH) in the diagnostic setting.
Methods: TMA constructs from 57 cases of breast cancer were evaluated for HER2 (by ICC and FISH) by two centres. The results were compared.
Results: There was a high level of concordance for both ICC and FISH. In five ''discrepant'' cases only three would have had a potential impact on patient management.
Conclusions: Validation of HER2 analysis in the clinical setting by ICC and FISH is essential. The use of TMAs provides for an economy of scale and would be practical in the setting of interlaboratory and intralaboratory validation. It is suggested that routine HER2 ICC and FISH should continue to be performed in laboratories on whole sections. Following this, TMAs would be constructed for all cases of breast cancer. ICC and FISH would be performed on these to validate the results. The TMAs would be available for circulation to other centres for validation purposes. The standardisation of testing between centres, the potential difficulty of minimum case numbers, and the workload issues surrounding validation would all be facilitated by this approach.

Two sets of guidelines impact on the use of HER2 testing in breast cancer in terms of immunocytochemical evaluation (ICC) and fluorescence in situ hybridisation (FISH). Guidelines from the National Institute for Clinical Excellence[1] state that FISH should be performed only on those cases that yield a 2+ score by ICC. UK best practice recommendations[2] support the use of validated ICC and FISH assays and these recommendations have recently been updated.[3] We describe an approach to validation using tissue microarrays (TMAs), which provides an efficient means of covering the range of HER2 ICC cases scoring from 0 to 3+.

> ''Tissue microarrays also allow for the large scale analysis of the HER2 gene by fluorescence in situ hybridisation''

TMA technology is increasingly being used in the research setting. Recent work in the department of pathology, Beaumont Hospital/RCSI, Ireland has shown that TMAs provide comparable results (to full sections) in the assessment of HER2.[4] TMAs also allow for the large scale analysis of the HER2 gene by FISH.[4 5] The potential for TMAs to provide a means for large scale validation of HER2 assessment by both ICC and FISH is clear. Our study describes a trial approach to the use of TMA as a validation tool for HER2 testing by both ICC and FISH.

METHODS

A comparative study was undertaken between two centres (University of Wales, Cardiff and Beaumont Hospital/RCSI, Dublin) contributing to regional HER2 testing by ICC and FISH. Both institutions use the HercepTest™ (Dako, Ely, Cambridge, UK) for ICC. FISH analysis at the University of Wales uses a one probe system provided by Benchmark™ and at the Royal College of Surgeons in Ireland (RCSI) a two probe system manufactured by Vysis™ (PathVysion HER2 DNA probe kit; Vysis Inc, Downers Grove, Illinois, USA) is used.

The specific goals were twofold:

(1) Validation of the Benchmark system for HER2 FISH analysis against the Vysis system.
(2) Evaluation of the interlaboratory reproducibility of the HercepTest in terms of technique and interpretation.

Specimen selection and processing

Fifty seven consecutive cases of breast cancer (55 ductal and two lobular carcinomas) from August 2000 to July 2001 with recorded HercepTest staining were selected from the files of the histopathology department of Beaumont Hospital. These cases had been reviewed previously as part of a comparison between ICC and ISH,[4] and the level of concordance between whole section and TMA ICC is detailed in that publication. The local ethics committee approved the study. The corresponding formalin fixed, paraffin wax embedded tissue blocks containing tumour material were retrieved from the archives, along with their respective haematoxylin and eosin and HercepTest stained sections. Using the haematoxylin and eosin stained slide as a template, representative areas of carcinoma were identified and marked. A tissue microarray was constructed by sampling four cores (0.6 mm diameter) from each block using the technique pioneered by Kononen *et al*.[6] Four cores were sampled from different tumour areas to account for heterogeneity in any one tumour and to minimise the number of lost cases during subsequent processing of the microarray. Cores were then introduced into a single empty recipient paraffin wax block and sections of the microarray were cut for the purpose of ICC and FISH staining.

Immunocytochemistry (HercepTest): RCSI and University of Wales

Sections (4 µm thick) of the tissue microarray were cut, mounted on Vectabond coated slides (Vector Laboratories Inc, Burlingame, California, USA), and dried overnight at

Abbreviations: ICC, immunocytochemistry; FISH, fluorescence in situ hybridisation; NEQAS, National External Quality Assurance Scheme; RCSI, Royal College of Surgeons in Ireland; TMA, tissue microarray

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50℃. Detection of the HER2 protein was carried out using the Dako HercepTest kit with a standard protocol according to the manufacturer's instructions. A supplied performance control slide containing three pelleted, formalin fixed, paraffin wax embedded cell lines was included in each staining procedure. The score for each of the cell lines was as follows: negative cell line (MDA-231), no membrane staining observed; 1+ cell line (MDA-175), faintly perceptible staining intensity with incomplete membrane staining present on small to moderate numbers of the cells; 3+ cell line (SK-BR-3), intense, complete membrane staining present on most of the cells. A ''mini'' array of eight breast cancer samples containing two examples of each staining pattern was also included as an in house tissue control. The negative control antibody provided in the kit was used for all test cases and the in house tissue control. Scoring of the immunocytochemical preparation was performed in masked fashion by three independent investigators (EK, AO'G, and BJ) on a 0 to 3 point scale using the manual for interpretation provided by the manufacturer (http://www.dakocytomation.com). For the purposes of Herceptin treatment, a HercepTest score of 0 or 1 is interpreted as negative for HER2 overexpression. An average score was calculated for each case in the TMA, with a score of 1.5 or greater designated as positive.

FISH (PathVysion HER-2 DNA probe kit): RCSI

The PathVysion HER2 DNA probe kit and paraffin wax pretreatment kit (Vysis Inc) were used in accordance with the manufacturer's recommended protocol using a 4 μm section of the TMA. Slides were stored at −20℃ in the dark before signal enumeration with a Nikon Eclipse E600 Microscope (Nikon Inc, Melville, New York, USA) using ×100 magnification (oil immersion) and appropriate multiband pass filters. Appropriate positive (HER2 gene amplification) and negative (non-amplification) control slides were included in the staining run. Analysis of the FISH score was carried out by comparing the ratio of the average copy number of the HER2 gene with that of the chromosome 17 centromere in 60 nuclei/case. Specimens with a signal ratio of more than 2 were scored as positive (HER2 amplified) and those with a signal ratio of less than 1.8 were scored as negative. Samples scoring between 1.8 and 2.2 were considered borderline and were re-enumerated.

Four TMA sections were cut and sent to the University of Wales College of Medicine and the immunocytochemistry and FISH testing was repeated using the HercepTest (according to the protocol outlined above) and the Benchmark system (according to the protocol outlined below).

FISH (Benchmark): University of Wales

Gene amplification was detected on the formalin fixed, paraffin wax embedded tissues with FISH using the Ventana Inform Her-2/neu probe assay system on a Benchmark automated instrument. The slides were then washed free of FISH reagents and mounted using Vectashield mounting medium containing propidium iodide (Vector Laboratories Inc). All slides were stored in light tight containers at −20℃ until examination using a Leica DMB microscope with a ×100 oil immersion lens. Standard controls included National External Quality Assurance Scheme (NEQAS) quality control cell lines with varying amounts of HER2 gene amplification, a known amplified breast tumour, and tonsillar (negative control) tissue. FISH signals were assessed by two independent assessors (JMM and BJ) examining 40 non-overlapping nuclei for each tissue. The results were graded as mean signals/cell: with < 4 as negative (grade 1), > 4 to $\leqslant 10$ as intermediate grade positive (grade 2), and > 10 as strong positive (grade 3).

RESULTS

Cases were selected for analysis if they had three or more adequate cores for interpretation. Of the 57 cases assembled in the TMA, three were excluded: one for technical reasons because of a loss of core or excessive folding, and two other cases because of insufficient tumour material ($< 20\%$ of the core) in two or more of four cores. Of the remaining 54 cases, 44 had four adequate cores for interpretation, and 10 had three adequate cores for interpretation. The total number of adequate cores for interpretation was 206 of a possible 216 (95%). Table 1 shows the overall results for each laboratory. These cases had been reviewed previously as part of a comparison between ICC and ISH,[3] and the level of concordance between whole section and TMA ICC is detailed in that publication.

There was a high level of concordance for both ICC and FISH between the two laboratories. Forty eight of 54 cases were concordant for both ICC and FISH between the two laboratories and, in the case of ICC, between TMA in both laboratories and whole section. Of the remaining six cases, one was not analysed by the University of Wales, Cardiff because no tissue remained in the TMA sections for that case. Therefore, there were five discrepant cases, which are detailed in table 2.

Case 7 showed discrepant ICC results on TMA. This was at the level of 1+/2+. FISH in both institutions showed no amplification. As a result there would have been no impact on the patient.

Case 34 showed discrepant ICC between the original whole section (2+) and the TMA in both institutions ($< 1+$ in each). FISH showed no amplification.

Case 32 is an example of where an original whole section ICC score of 3+ was not supported by FISH amplification. If a policy of only performing FISH on 2+ ICC cases were to be standard practice, this patient would have been inappropriately recommended for Herceptin treatment.

Case 52 is complex. At the RCSI the 3+ original score would have been backed up by FISH amplification. The variability in ICC score on the TMA cores is worthy of note and the mean score of 1.25 would not have led to referral for FISH analysis. Furthermore, at the University Hospital of Wales the original 3+ score (from the Dublin archive) was not followed by amplification by FISH. This in itself is a problem, in addition to the fact that FISH analysis gave differing results in the two laboratories.

In case 53, the 3+ ICC original score was supported by FISH amplification (intermediate grade positive) at the University Hospital of Wales. At the RCSI, the FISH results were ''borderline'', which is always a difficult area for interpretation. The 2+ ICC score on the TMA cores is of interest in terms of this ''borderline'' result. From the patient's point of view in this case the 3+ ICC score would have led directly to a recommendation for Herceptin treatment.

DISCUSSION

This trial approach to the use of TMA as a potential tool for the validation and interpretation of HER2 ICC and HER2 FISH analysis shows a high level of concordance for both techniques between the two laboratories. Clearly, the use of TMA in this setting provides for an economy of scale on the one hand, with at least 50 cases arrayed on a single slide, while at the same time addressing the issue of a large volume workload for reliable HER2 analysis and reporting.[6] The results seen here are promising in terms of using this technique for both interlaboratory and intralaboratory validation. The use of four cores for each case is accepted as being representative,[7–9] and the level of concordance between ICC on whole sections and TMA and between ICC and FISH has been previously established,[4 5] although it must

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Table 1 Data on each case from both laboratories

Case	Hercep (section)	Core	Hercep (Cardiff)	Hercep (RCSI)	FISH (Cardiff)	FISH (RCSI)
1	1+	1	0	0	1	0.99
		2	0	0	1	
		3	0	0	1	
		4	X	X	X	
2	3+	1	3	3	3	6.03
		2	3	3	3	
		3	3	3	3	
		4	3	3	3	
3	3+	1	X	X	X	2.64
		2	3	3	3	
		3	3	3	2	
		4	3	3	1	
4	Negative	1	0	0	X	1.02
		2	X	0	X	
		3	X	0	1	
		4	1	0	1	
5	Negative	1	1	X	1	0.89
		2	1	0	1	
		3	0	0	1	
		4	0	0	1	
6	3+	1	3	3	3	3.55
		2	3	3	3	
		3	X	X	X	
		4	3	3	3	
7	2+	1	2	1	1	1.59
		2	2	1	1	
		3	2	1	1	
		4	2	1	X	
8	3+	1	3	3	3	8.21
		2	3	3	3	
		3	3	3	3	
		4	3	3	3	
9	3+	1	3	3	3	6.12
		2	3	3	3	
		3	3	2	3	
		4	3	3	3	
10	Negative	1	0	0	1	0.89
		2	0	X	0	
		3	0	0	1	
		4	1	1	1	
11	Negative	1	1	0	1	0.9
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
12	Negative	1	0	0	1	0.86
		2	0	0	1	
		3	1	0	1	
		4	0	0	1	
13	Negative	1	0	0	1	0.8
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
14	Negative	1	0	0	1	0.91
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
15	Negative	1	0	0	1	0.94
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
16	2+	1	2	2	1	0.83
		2	1	1	1	
		3	1	X	1	
		4	2	2	1	
17	3+	1	3	3	3	4.89
		2	3	3	3	
		3	3	3	3	
		4	3	3	3	
18	Negative	1	0	0	1	0.82
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
19	1+	1	2	1	2	1.22
		2	1	1	1	
		3	1	1	1	
		4	1	1	1	
20	Negative	1	0	0	1	0.97
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
21	Negative	1	1	1	1	0.93
		2	1	1	1	
		3	1	1	1	
22	Negative	1	0	0	1	0.67
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
23	Negative	1	1	1	1	0.84
		2	1	1	1	
		3	0	0	1	
		4	0	0	1	
24	Negative	1	1	1	1	0.94
		2	1	1	1	
		3	1	1	1	
		4	1	1	1	
25	Negative	1	0	0	1	0.83
		2	0	0	1	
		3	0	0	1	
		4	X	0	X	
26	3+	1	3	3	3	8.59
		2	3	3	3	
		3	3	3	3	
		4	2	3	2	
27	Negative	1	0	0	1	0.83
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
28	Negative	1	0	0	1	0.98
		2	0	0	1	
		3	0	0	1	
		4	1	1	1	
29	Negative	1	0	0	1	0.83
		2	1	1	1	
		3	0	0	1	
		4	0	0	0	
30	3+	1	3	3	3	2.67
		2	3	3	3	
		3	3	3	3	
		4	3	3	3	
31	Negative	1	0	0	1	1.03
		2	0	1	1	
		3	0	0	1	
		4	0	1	1	
32	3+	1	2	2	1	0.94
		2	2	2	2	
		3	0	1	2	
		4	2	1	2	
33	Negative	1	1	1	1	0.86
		2	1	1	1	
		3	0	0	1	
		4	1	0	1	
34	2+	1	1	0	X	0.85
		2	1	X	1	
		3	1	1	1	
		4	0	0	0	
35	Negative	1	0	1	0	0.7
		2	0	1	0	
		3	1	1	1	
		4	0	1	0	
36	Negative	1	0	0	0	0.68
		2	X	0	0	
		3	0	X	0	
		4	X	0	0	
37	Negative	1	X	X	X	0.87
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
38	3+	1	3	3	3	12
		2	3	3	3	
		3	3	3	3	
		4	3	3	3	
39	Negative	1	0	0	0	0.79
		2	0	0	0	
		3	0	0	1	
		4	0	0	1	
40	Negative	1	0	0	0	0.81
		2	0	0	0	
		3	0	0	1	
		4	0	0	1	

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Table 1 Continued

Case	Hercep (section)	Core	Hercep (Cardiff)	Hercep (RCSI)	FISH (Cardiff)	FISH (RCSI)
41	Negative	1	1	1	1	0.79
		2	2	2	0	
		3	X	1	X	
		4	1	1	1	
42	1+	1	0	0	1	0.75
		2	0	0	1	
		3	0	0	0	
		4	0	1	0	
43	Negative	1	0	0	1	0.82
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
44	Negative	1	0	0	1	0.8
		2	0	0	0	
		3	0	0	0	
		4	0	0	0	
45	Negative	1	0	0	0	0.89
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
46	Negative	1	0	0	1	0.87
		2	0	0	1	
		3	0	0	1	
		4	X	0	1	
47	Negative	1	0	0	1	1.19
		2	0	0	1	
		3	0	0	1	
		4	0	0	0	
48	1+	1	0	0	1	0.8
		2	0	0	X	
		3	0	0	0	
		4	0	0	1	
49	Negative	1	0	0	1	0.98
		2	0	0	1	
		3	0	0	1	
		4	X	0	1	
50	1+	1	0	1	1	1.15
		2	0	0	1	
		3	0	0	1	
		4	0	0	1	
51	1+	1	0	0	1	0.85
		2	0	0	1	
		3	X	0	1	
		4	0	0	1	
52	3+	1	X	2	2	3.01
		2	X	2	2	
		3	0	1	1	
		4	X	0	1	
53	3+	1	X	2	2	1.99 (1st)
		2	0	2	1	1.97 (2nd)
		3	0	2	3	
		4	2	2	2	
54	Negative	1	X	0	X	0.86
		2	X	X	X	
		3	X	0	X	
		4	X	0	X	

X, no data available because (i) there was no core present, (ii) there was no tumour present in the core, or (iii) there was excessive folding/lifting of tissue that prevented accurate assessment of the HercepTest/FISH score. FISH, fluorescence in situ hybridisation.

be accepted that concordance alone based on the validation of techniques is not a measure of clinical relevance or outcome.

Technical validation is a concept widely accepted in laboratory practice and such quality assurance and quality control is currently provided for via UK NEQAS. TMA validation as described could also provide for interpretive quality assurance/quality control, which is not at present available via UK NEQAS. Given the subjective nature of HER2 ICC assessment, such interpretive validation would be valuable.

We suggest that routine HER2 ICC and FISH should continue to be performed in laboratories on whole sections, following which, reference centres such as those involved in our study would construct TMAs of all breast cancer cases, exchange them for HER2 ICC and FISH testing, and also make them available for circulation to other (perhaps smaller) centres for validation purposes. FISH testing (the currently accepted ''gold standard'') would be performed on all cases using this model.

> ''The standardisation of testing between centres, the potential difficulty of minimum case numbers within any given laboratory, and the workload issues surrounding validation would all be facilitated by the approach outlined in our study''

In the setting of HER2 ICC and FISH analysis there is clearly a need for serial validation to supplement the current cell line standard developed and distributed by UK NEQAS for ICC.[10] The construction of TMAs in a ''reference'' centre would produce approximately four TMAs each year (representing 200 cases), and these would then lead to the existence of a valuable resource for circulation for the purpose of ongoing validation, both technical and interpretive. The expertise and infrastructure of UK NEQAS in such a programme would seem both valuable and sensible. In time, the TMA constructs would represent a large pool of cases representing all categories of HER2 ICC score (0 to 3+) from several centres, with their different fixation schedules and with a wide range of patient details, in particular age.

Issues such as fixation, effect of age on expression levels, and any other variables would consequently be captured in this ongoing validation exercise.

Ultimately, the opportunity for the TMA constructs to represent clinically validated cases would further strengthen the process. The standardisation of testing between centres, the potential difficulty of minimum case numbers within any given laboratory, and the workload issues surrounding validation would all be facilitated by the approach outlined in our study.

In addition to the validation issues, the TMA approach would also allow several other questions to be answered in time, specifically:

Take home messages

- Validation of HER2 analysis in the clinical setting by immunocytochemistry (ICC) and fluorescence in situ hybridisation (FISH) is essential
- Using tissue microarrays (TMAs), we found that there was a high level of concordance for both techniques between the two laboratories tested
- Therefore, the use of TMAs would be economical and practical for interlaboratory and intralaboratory validation
- We propose that routine HER2 ICC and FISH should be performed on whole sections, with TMAs being constructed for all cases of breast cancer, and ICC and FISH being carried out on these to validate the results
- The TMAs should be available for circulation to other centres for validation purposes. The standardisation of testing between centres, the potential difficulty of minimum case numbers, and the workload issues surrounding validation would all be facilitated by this approach

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Table 2 Discrepant cases and impact on patient management

		TMA				
		ICC		FISH		
Case	Section ICC	RCSI mean score (score/core)	UHW mean score (score/core)	RCSI	UHW mean grade (individual grades)	Potential impact on decision to offer Herceptin treatment
7	2+	1 (1, 1, 1, 1)	2 (2, 2, 2, 2)	1.59	0.75 (1, 1, 1, 0)	None
32	3+	1.5 (2, 2, 1, 1)	1.75 (2, 2, 0, 2)	0.94	1.75 (1, 2, 2, 2)	*
34	2+	0.3 (–, 0, 1, 0)	0.75 (1, 1, 1, 0)	0.85	0.67 (–, 1, 1, 0)	None
52	3+	1.25 (2, 2, 1, 0)	NT (–, –, –, 0)	3.01	1.5 (2, 2, 1, 1)	†
53	3+	2 (2, 2, 2, 2)	0.3 (–, 0, 0, 2)	1.99 and 1.97	2 (2, 1, 3, 2)	‡

*Although the RCSI results revealed no amplification by FISH the whole section score of 3+ and the amplification revealed by the Ventana probe meant that the patient would have been recommended for treatment, presumably inappropriately; †no patient impact at the RCSI but impact at the UHW. The UHW TMA ICC was non-contributory. The individual ICC scores for each core at the RCSI are of interest in terms of the absence of amplification determined at the UHW; ‡This is clearly a difficult case, where FISH testing produced a borderline result on two occasions at the RCSI. It is of interest that the 4 cores gave a score of 2+ by ICC. In both institutions the patient would have received Herceptin treatment.
ICC, immunocytochemistry; FISH, fluorescence in situ hybridisation; NT, no tumour remaining; RCSI, Royal College of Surgeons in Ireland; TMA, tissue microarray; UHW, University Hospital of Wales.

(1) Whether FISH is required only on ICC 2+ cases, or whether, as we currently advocate, it should be performed on all cases.
(2) The level of heterogeneity within cases and its impact.
(3) The clinical impact of HER2 result accuracy, gene status as measured by FISH, and HER2 protein status as measured by ICC.

SUMMARY

The debate continues in the literature as to the most accurate determination of HER2 status in breast cancer.[11 12] Working with the current guidelines in the UK,[1 3] we present the results of a trial approach to the validation of HER2 assessment in breast cancer using TMAs constructed in ''reference'' laboratories and suggest that this approach would provide an accurate and economical method for interlaboratory and intralaboratory validation in this setting.

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