Consistency of microstaging pT1 bladder transitional cell carcinoma

Transitional cell carcinoma is a common tumour, with over 10 000 cases diagnosed each year and almost 5000 deaths. Traditional prognostic factors are grade, stage, size, multiple tumours, bladder neck involvement and age, and the tumour, node, metastasis criteria[1] for staging are widely accepted. Tumours invading the subepithelial connective tissue are classified as pT1. Publications have looked at the depth of infiltration of transitional cell carcinoma with infiltration of the lamina propria for about 10 years.[2–7] The publication of Scottish Intercollegiate Guidelines Network (SIGN) guideline 85 ''Management of Transitional Cell Carcinoma of the Bladder''[8] cites two references as evidence of microstaging being an independent prognostic variable. However, there was concern after the publication of this guidance that there would be significant training requirements for histopathologists and concerns regarding the consistency of interpretation. Furthermore, published literature includes different staging systems for pT1 transitional cell carcinoma including a two-stage and a three-stage system. The three-stage system is variably defined; although all systems show prognostic information, one three-stage system was adopted here as it was believed to be the most straightforward (table 1).

It was thought important to test the consistency of microstaging of transitional cell carcinoma by general pathologists before the roll-out of microstaging by the West of Scotland Urology Cancer Network. The aim of this study was therefore to determine whether general pathologists were able to reproducibly microstage pT1 transitional cell carcinoma of the bladder and whether the two-stage or three-stage system was more consistent (table 1). Another aim of the study was to see whether pathologists were reliably able to recognise muscularis mucosae and whether this affected the microstaging.

Methods

Using records from the weekly urology multidisciplinary team meetings for NHS Ayrshire and Arran, a list of all the pT1 transitional cell tumours diagnosed between January 2000 and April 2006 at Ayr Hospital, Ayr, UK were obtained. Slides from all 75 cases (55 patients) were examined by LC and ERN and microstaged according to both the two-tier and three-tier systems defined by the SIGN guideline 85. Of the 75 cases, 7 were excluded because cautery artefacts or other artefacts made it impossible to determine the exact level of the invasion. Cases were then selected according to the following criteria:

- disagreement between the initial assessors
- possible problems in interpreting the size of blood vessels
- exclusion of most simple pT1a cases.

There was a deliberate attempt to increase the proportion of difficult cases, as it was thought that recognition of pT1a cases would be straightforward. A particular problem with the initial selection was the definition of the thick-walled blood vessels deep in the lamina propria.

Thirty-one representative slides were then anonymised and independently microstaged by six general pathologists at Crosshouse Hospital, Kilmarnock, UK, using both two-tier and three-tier systems. The presence or absence of the muscularis mucosae was also noted. This staging followed a presentation of the staging systems as described by the SIGN guideline. The guidance issued is reproduced here (table 1) and was issued to the pathologists; no further training was given.

The data were then analysed using SPSS V.13.0. The degree of concordance between pathologists was assessed using the κ statistic. A κ score between 0.4 and 0.59 indicated moderate agreement and a score of between 0.6 and 0.79 indicated substantial agreement (a score of 0 means that the observed agreement is no better than chance and 1 means perfect agreement).[9]

In the three-tier system, disagreement between pathologists can be by one tier (eg, one pathologist microstages a tumour as pT1a and the other as pT1b) or by two tiers (eg, one pathologist microstages a tumour as pT1a and the other as pT1c). In this case a weighted κ[10] was used.

Results

Table 2 compares the concordance between each of the six pathologists (A–F) for the two-tier system using κ. The table also gives the number of slides for which there was agreement between the pathologists.

For the two-tier system of microstaging (pT1a and 1b), κ scores between pairs of pathologists range from 0.403 to 0.784, with a median score of 0.623. There are 15 possible combinations of pairs of pathologists and 7 of these 15 pairs show moderate agreement whereas 8 pairs show substantial agreement. The actual number of agreements and disagreements between each pair is also shown. Overall, for the two-tier system there were 374 agreements of a possible 465 comparisons, which meant there was agreement between pathologists on 80.43% of occasions. The median κ score was 0.623, which indicates substantial agreement.

Table 3 shows the concordance between pairs of pathologists using the three-tier system. For the three-tier system, weighted κ scores between the pairs of pathologists were slightly lower, ranging between 0.420 and 0.677, with a median score of 0.566. Of the 15 pairs, 8 showed moderate agreement whereas 7 pairs showed substantial agreement. Overall, using the three-tier system there was agreement on 66.88% of occasions (311 of 465 possible agreements). Of the disagreements, 142 of 154 are by a factor of 1 (92%) and only 12 (8%) by a factor of 2.

Overall, there is a reasonable level of consistency across all six pathologists. This is illustrated by the fact that if the two pathologists with the lowest consistency overall are excluded from the results (pathologists A and E) this only increases the median κ score for the two-tier system from 0.623 to 0.664, with an overall agreement of 86.02%. For the three-tier system the median κ score only increases from 0.566 to 0.574, with an overall agreement

Table 1 Stratification of pT1 bladder TCC into two-tier[2] and three-tier systems[5]

	Two-tier system	Three-tier system
pT1a	Invasion of papillary stalk or into lamina propria at base of tumour	Invasion of papillary stalk but not beyond base of tumour
pT1b	Invasion into muscularis mucosae or around thick-walled blood vessels deep in lamina propria	Invasion into lamina propria at base of tumour
pT1c		Invasion into muscularis mucosae or around thick-walled blood vessels deep in lamina propria

Table 2 Concordance between pairs of pathologists using two-tier microstaging

Rater 1	Rater 2	κ	Agreement	Disagreement
A	B	0.535	24	7
A	C	0.403	22	9
A	D	0.599	25	6
A	E	0.553	24	7
A	F	0.459	23	8
B	C	0.718	27	4
B	D	0.640	26	5
B	E	0.623	25	6
B	F	0.625	26	5
C	D	0.784	28	3
C	E	0.623	25	6
C	F	0.625	26	5
D	E	0.563	24	7
D	F	0.688	27	4
E	F	0.445	22	9
Mean		0.592	24.93	6.07
Median		0.623	25	6
Minimum		0.403	22	3
Maximum		0.784	28	9
SD		0.103		
Total			374	91
Percentage			80.43%	19.57%

Table 3 Concordance between pairs of pathologists using the three-tier system

Rater 1	Rater 2	Weighted κ	Agreement	Disagreement	
				By one tier	By two tiers
A	B	0.478	17	14	0
A	C	0.420	19	10	2
A	D	0.518	20	10	1
A	E	0.634	22	9	0
A	F	0.613	22	9	0
B	C	0.544	20	10	1
B	D	0.481	19	10	2
B	E	0.604	20	11	0
B	F	0.645	22	9	0
C	D	0.516	19	12	0
C	E	0.566	22	7	2
C	F	0.603	23	7	1
D	E	0.498	20	9	2
D	F	0.621	23	7	1
E	F	0.677	23	8	0
Mean		0.561	20.73	9.47	0.80
Median		0.566	20	9	1
Minimum		0.420	17	7	0
Maximum		0.677	23	14	2
Total			311	142	12
Percentage			66.88%	30.54%	2.58%

Table 4 Differences in the identification of the muscularis mucosae

Pathologist	MM present	MM absent
A	17	13
B	9	22
C	19	12
D	7	24
E	16	15
F	26	5

MM, muscularis mucosae.

of 67.74%, which represents moderate agreement.

Table 4 shows the assessment of whether the muscularis mucosae was present or not, and this varies from 29% to 84%. All six pathologists agreed that the muscularis mucosae was present in only 12% of cases.

Discussion

Patients with a superficial transitional cell carcinoma (in situ and invasion of the lamina propria) have a 5-year survival of 80–90% compared with <50% for muscle invasive carcinoma.[11] However, superficial transitional cell carcinomas can behave very differently, which is reflected in their varying levels of recurrence and progression. This has led to the recommendation that pT1 transitional cell carcinomas should be microstaged according to the depth of invasion of the lamina propria.

Both the two-stage and three-stage systems show statistically significant differences in recurrence and progression. The two-stage system reported by Sozen *et al*[2] quotes recurrence and progression rates of 32% and 5.8% for pT1a and 62% and 37.5% for pT1b carcinomas, respectively. One three-stage system[6] similar to that used here reported recurrence and progression rates of 49% and 6% for pT1a, 58% and 33% for pT1b, and 59% and 55% for pT1c disease, respectively. Herman *et al*,[5] using the same three-stage system as used here, showed survivals of 79% for pT1a, 70% for pT1b and 57% for pT1c.

Different definitions for three-tier microstaging pT1 carcinomas are present in the literature, with resultant confusion as to the exact definitions, and it is believed that a single system should be selected and used nationally. This should be simple, reproducible and prognostically relevant. Other studies of consistency have indicated that two categories are more reproducible than three categories, and in this study there is a higher level of agreement with a two-stage system. This could be included in a revision of the Royal College of Pathologists Minimum Dataset for Bladder Cancer[12] or through the recently formed British Association of Urological Pathologists. Limited training was given to the pathologists in this study with good results. It is likely that similar illustrations and definitions would produce the same result if this were adopted nationally and formal teaching would seem unnecessary.

Although there was initial scepticism that non-specialist pathologists could reproducibly microstage pT1 bladder carcinomas, this study has shown that pathologists can achieve good consistency rates even where some of the most straightforward (pT1a) cases have been excluded and where the most difficult cases deliberately included. However, a small percentage of specimens cannot be microstaged, often because of cautery artefact and in our study this was around 10%.

Muscularis mucosa is variably present in the bladder, with reports varying from 35% to 70%, and may be a complete layer, a partial layer or a minimal layer.[13] There was substantial disagreement regarding the presence or absence of muscularis mucosae in this study, but there was still a moderate agreement for the three-tier microstage system. The superficial lamina propria at the base of the tumour is relatively easy to recognise and the two-tier system is simpler to use in practice as it mostly avoids having to recognise the depth of invasion of the lamina propria. It was difficult to differentiate the thick-walled vessels of the deep lamina propria from more superficial dilated vessels. It is therefore recommended that microstaging of pT1 transitional cell carcinomas of the bladder using a two-stage system be incorporated into routine pathological practice.

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