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Clinical importance of squamous metaplasia in invasive transitional cell carcinoma of the bladder

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SUMMARY One hundred cases of transitional cell carcinoma of the bladder were studied to determine whether squamous metaplasia and other histological features within the bladder can be of value in predicting outcome of treatment with radiotherapy. Sixty cases showed the changes of squamous metaplasia, and of this group 46 (78%) failed to respond to radiotherapy. A significant response rate of 90% was seen in the 40 tumours without squamous metaplasia.

It is concluded that transitional cell carcinomas of the bladder showing squamous metaplasia are mainly resistant to radiotherapy and alternative treatment methods should be sought.

The heterogeneity of invasive bladder carcinoma has prompted many studies of histological features in an attempt to relate these to prognosis.[1-3] Most studies have been performed on radical cystectomy specimens, and there is little information about the histological features in transurethral resection material which may be relevant to the prognosis of patients, especially those treated with radiotherapy.

The presence of squamous metaplasia is well recognised in transitional cell carcinoma of the bladder,[4,5] but its importance for prognosis is not known. It has been shown that squamous cell carcinoma of the bladder is more resistant to radiotherapy than its transitional cell counterpart,[6,7] and this aroused our interest in the responsiveness to radiotherapy of transitional cell carcinomas showing squamous metaplasia.

It has been suggested that if radioresponsiveness of the tumour could be predicted more accurately before irradiation then non-responders could be offered alternative treatment including early cystectomy. We therefore undertook a study to determine whether the histological features of invasive transitional cell carcinoma of the bladder were related to or could be used to predict the response of the tumour to radiotherapy.

Material and methods

From the records of the departments of urology and histopathology at this hospital 111 patients with muscle invasive transitional cell carcinoma of the bladder were identified (International Union Against Cancer (UICC) and American (Jewett) classification stage T2/T3).[1] These patients presented between 1980 and 1985 and had received radiotherapy. Six cases with invasion of the prostate (UICC stage 4) were excluded as this group is recognised as having a poor prognosis and as being resistant to radiotherapy.[8] In five cases the original pathology material was unavailable, thus leaving 100 cases. The mean age of patients was 68·3 years, range 33–85. There were 78 men and 22 women.

The histological sections were processed from tissue fixed in 10% formol saline by standard techniques and stained with haematoxylin and eosin. The original tumours before treatment had been reviewed independently by three pathologists (JM, RZ, SB) unaware of the clinical outcome. Between one and seven blocks of tissue were available in each case (mean 2·6).

The sections were assessed for grade using the WHO classification,[5] degree and type of inflammatory cell infiltrate, the presence of necrosis, the presence of carcinoma in situ adjacent to the tumour, papillary or solid growth pattern, vascular invasion and the presence of squamous metaplasia within the tumour.[5] Squamous metaplasia was diagnosed using the usual criteria including abundant eosinophilic cytoplasm, large oval nuclei with an open chromatin pattern and prominent nucleoli. Cellular alignment, intercellular bridges, and keratin production were also useful features. The extent of squamous metaplasia was classified in three groups. Tumours were therefore graded 0 (no squamous metaplasia), 1–3 (small, moderate, or extensive areas of squamous metaplasia) initially, and then simply +(0)/–(1–3) for further statistical analysis.

The results were correlated with the response to radiotherapy, as judged on subsequent cystoscopy and

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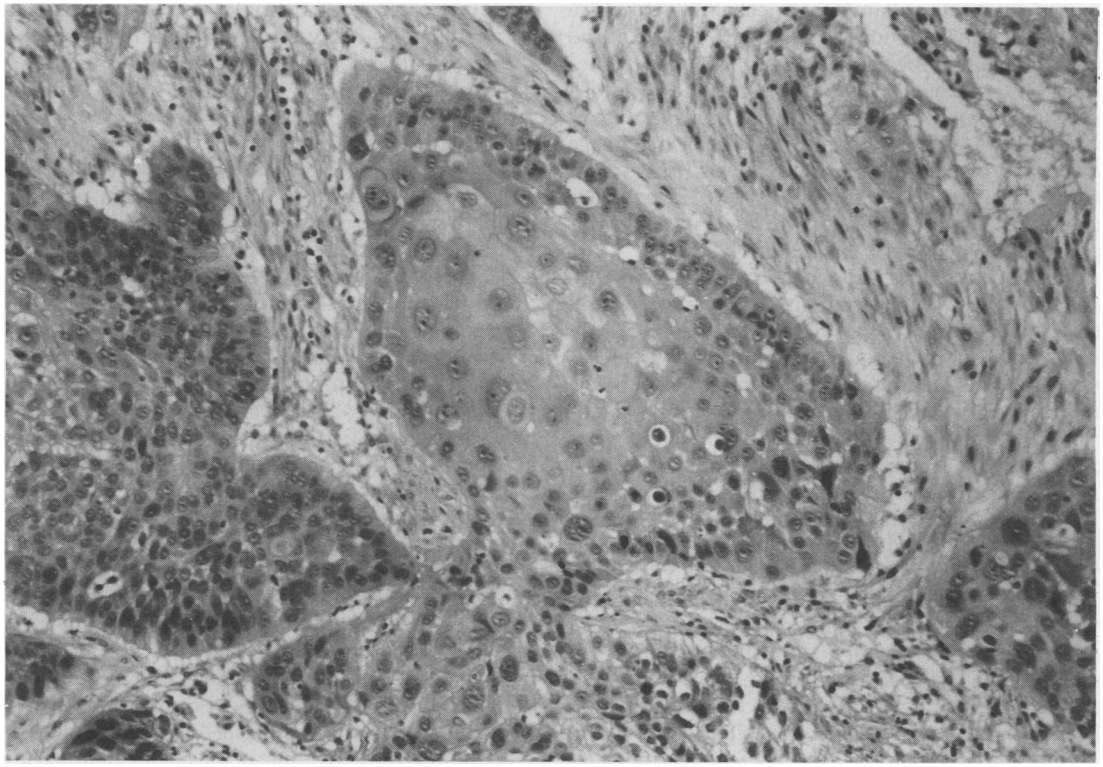

Figure *Poorly differentiated transitional cell carcinoma showing island of squamous metaplasia.*

rebiopsy at three and six months after treatment. Statistical techniques with multifactorial analysis and the χ^2 test were applied to the findings.

Results

Ninety two patients had grade 3 tumours and eight grade 2. There were no grade 1 tumours (table 1). All tumours were T2/T3 stage which was confirmed on histological examination. Sixty tumours showed areas of squamous metaplasia (figure).

Seven tumours showed no clinically important inflammation. Seventy five showed mild, 17 moderate, and one pronounced inflammation. Two tumours

Table 1 *Histological features in transitional cell carcinoma of bladder*

Grade of tumour		*Grade 2*	*Grade 3*	*Total*
Number		8	92	100
Response to radiotherapy	Positive	4	45	49
	Negative	4	47	51
Squamous metaplasia	Positive	4	56	60
	Negative	4	36	40
Necrosis	Positive	2	51	53
	Negative	6	41	47
Field change	Positive	2	53	55
	Negative	6	39	45
Inflammatory grade*	0	1	6	7
	1	7	68	75
	2	0	17	17
	3	0	1	1
Inflammatory type†	0	1	6	7
	Acute	2	2	4
	Mixed	1	44	45
	Chronic	6	40	46

*0 = no clinically important inflammation, 1 = mild, 2 = moderate, 3 = severe. †0 = no inflammation.

showed an acute inflammatory cell infiltrate, 46 a chronic, mainly lymphocytic infiltrate, and 45 a mixed pattern. One tumour had a dense infiltrate of eosinophils. The presence of lymphoid aggregates was also noted adjacent to the tumour in 21 cases. Areas of necrosis were seen in 53 tumours. The "field" change of adjacent carcinoma in situ (CIS) was seen around 56 tumours. Forty five tumours showed a papillary surface and 55 were solid. Small vessel invasion was seen in 49 cases.

Forty nine tumours responded to radiotherapy with no residual tumour apparent at cystoscopy and rebiopsy (complete response) (table 2).

Statistical analysis showed no significant differences between grade 2 and grade 3 tumours for each of the features studied, including responsiveness to radiotherapy. A significant correlation ($p < 0.005$) was found between the presence of squamous metaplasia and the lack of response to radiotherapy. The degree of squamous metaplasia did not have any added significance. Of the 60 tumours showing squamous metaplasia, 47 (78·3%) failed to respond to radiotherapy. The 40 tumours showing no squamous metaplasia had a radiotherapy response rate of 90%, with only four of 40 (10%) tumours failing to respond. The sensitivity of the presence of squamous metaplasia for predicting failure of response to radiotherapy was 92% (47/51) and the specificity was 78·3% (47/50).

Using a multivariant analysis, there was no correlation with any other histological feature studied and the response to radiotherapy or with each other. The presence of squamous metaplasia was not related to the presence of an inflammatory cell infiltrate, necrosis, or adjacent CIS.

Discussion

The corrected actuarial five year survival of patients with invasive transitional cell carcinoma of the urinary bladder treated with radiotherapy is 40%. A close correlation between survival and the initial responsiveness of transitional cell carcinoma to radiotherapy has also been shown.[9] In patients with tumours responding to radiotherapy the five year survival is 58%, with a corresponding rate of 21% for non-responders.[8 9] At the London Hospital 50% of patients with invasive transitional cell carcinoma show an initial complete response to radiotherapy. These figures are supported by data from groups with similar experience.[10 11] There is a need to identify the tumours that will respond to irradiation, but little progress has been made in this area so far.[12]

Several studies have attempted to relate the histological findings in bladder carcinoma to prognosis after cystectomy,[2 3 12] with varied results. Most studies have used an initial study population that is itself heterogeneous with respect to histological type and stage of tumour, and in some cases treatment. We studied a population of patients with stage T2/T3 disease and tumours of transitional cell type to try to eliminate variables recognised as independently influencing prognosis. We therefore excluded T4 tumours, adenocarcinomas, and pure squamous cell carcinomas.[6 8 13] Our group of patients was treated with radiotherapy and salvage cystectomy,[9] and histological studies were made on material from transurethral resection of tumour before irradiation.

Squamous cell carcinoma of the bladder is much less common in the United Kingdom than transitional cell carcinoma, but the prognosis is poor,[6] and the tumours are resistant to radiotherapy. The currently advocated treatment for squamous cell tumours is therefore radical surgery.[7] There have been no large studies of the responsiveness of transitional cell carcinoma showing squamous metaplasia to radiotherapy and the present trend is to treat them as a single group with those tumours not showing this feature.[8 9 11] It is only relatively recently that histopathologists have

Table 2 *Correlation of various histological features*

Grades 2 and 3 tumours		*Response to radiotherapy*		*Squamous metaplasia*		*Field change*		*Necrosis*		*Vessel invasion*		*Growth pattern*	
		Positive	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*
Response to radiotherapy	Positive	49		13	36	26	23	25	24	22	27	22	27
	Negative		51	47	4	29	22	28	23	27	24	23	28
Squamous metaplasia	Positive	13	47	60		36	24	33	27	35	25	26	34
	Negative	36	4		40	19	21	20	20	14	26	19	21
Field change	Positive	26	29	36	19	55		30	25	29	26	25	30
	Negative	23	22	24	21		45	23	22	20	25	20	25
Necrosis	Positive	25	28	33	20	30	23	53		23	30	17	36
	Negative	24	23	27	20	25	22		47	26	21	28	19
Vessel invasion	Positive	22	27	35	14	29	20	23	26	49		21	28
	Negative	27	24	25	26	26	25	30	21		51	24	27
Growth pattern	P	22	23	26	19	25	20	17	28	21	24	45	
	S	27	28	34	21	30	25	36	19	28	27		55

P = Papillary surface, S = Solid.

recognised that transitional cell carcinoma with squamous areas is an entity distinct from squamous cell carcinoma.[4,5]

Our findings indicate that the presence of squamous metaplasia within a tumour is associated with a poor response to radiotherapy. This agrees with the work of Tannenbaum *et al.* Other methods of treatment, including chemotherapy and partial and total cystectomy, may give better results in this group than those currently in use.

It was considered important to try to exclude the possibility that the squamous metaplasia in transitional cell carcinoma was a reaction to necrosis or inflammation. Squamous metaplasia affecting non-neoplastic epithelium is commonly seen in the bladder in response to calculi or chronic inflammation. The prostate may also show this change around areas of infarction and inflammation. Our results showed no correlation between the presence of squamous metaplasia and these other histological features, and we therefore conclude that squamous metaplasia marks a specific phenotypic variant of transitional cell carcinoma.

Our results show no evidence that tumours with a papillary surface respond better to radiotherapy. This finding does not support those of Slack and Prout or Shipley *et al,* but is in agreement with the findings of Boileau *et al.* We attempted to exclude the possibility that papillary growth was associated with more superficial growth and invasion, as suggested by Soto *et al,*[14] as well as by Slack and Prout, by ensuring that all patients had histologically confirmed T2/T3 tumours.

We also found no correlation between small vessel invasion and the response to radiotherapy, with a similar percentage of tumours showing this feature to those reported in other studies.[15-17] The lack of association between vessel invasion and response to radiotherapy is supported by the study of Pomerance on blood vessel invasion and prognosis.

In conclusion, we found that the presence of squamous metaplasia within invasive transitional cell carcinoma of the bladder is associated with failure of response to radiotherapy in 78% of cases, and that absence of this change is associated with a 90% complete response. The presence of squamous metaplasia in these tumours is not related to the presence of inflammation or necrosis but may be an expression of tumour phenotype. We suggest that histopathologists and urologists should place greater emphasis on the reporting of squamous metaplasia within transitional cell tumours. If our findings are confirmed in further studies radiotherapy may be shown to be inappropriate treatment for patients with transitional cell carcinoma showing this feature.

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