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MUCOSAL BIOPSIES FROM PATIENTS WITH TRANSITIONAL CELL CANCER OF THE BLADDER*

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Flat carcinoma *in situ* (TIS) was first described by Melicow[1] who examined sections of mucosa between gross neoplasms in cystectomy specimens. The clinical significance of these lesions has been clarified by later studies. In 1960 Eisenberg et al[2] reported that patients with mucosal abnormalities peripheral to excised papillary tumors were more prone to develop tumor recurrences. It was subsequently shown by Koss et al[3] that men exposed in industry to para-amino-diphenyl and who were shedding cancer cells in the urine had flat carcinoma *in situ* in the absence of cystoscopically visible tumors. In some cases these lesions progressed to invasive cancer. In 1979 Koss[4] reported further mapping studies and concluded that there are two pathways in bladder neoplasia: the papillary pathway and the non-papillary pathway. Papillary tumors with thin stalks were considered as local expressions of the proliferative potential of the urothelium, which although harmless may be followed by other manifestations of neoplasia. However, Koss considered non papillary flat lesions, notably atypical hyperplasia and carcinoma *in situ*, as the principle source of invasive carcinoma. The concept that the papillary tumor is a marker of the malignant potential of the epithelium but that most invasive tumors arise from flat carcinoma *in situ* is substantiated by a number of studies[5-7]. The time between progression from *in situ* to invasive carcinoma has been reported as being between 26 and 30 months[8], and between 18 and 77 months[3] but may be much longer.

The question remains whether a program of routine biopsy of cystoscopically looking normal mucosa in new bladder tumor cases will yield results which will improve management. The preliminary results of a prospective surveillance study where mucosal biopsies were obtained from 1) adjacent to the original tumor, 2) lateral to each ureteric orifice, and 3) the posterior mid-line, have been reported[9]. These preliminary results suggest that the presence of hyperplasia, dysplasia and carcinoma *in situ* may predict subsequent tumor recurrence. Two other studies also

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report this view. Wolf and Hojgaard[10] reported 53 patients with T1 or T2 tumors. In half of the cases there was concomitant urothelial dysplasia and it was found that new tumors occurred in 87% compared with 26% of the cases without any mucosal change. Schade and Swinney[11] reported the ten-year follow-up of 100 patients who were assessed with mucosal biopsy as part of their initial assessment. The outstanding finding was that patients with carcinoma *in situ* (40%) had a significantly worse outcome statistically than those with normal mucosa regardless of the characteristics of the primary tumor and its grade or stage ($p < 0.001$). The predictive value of mucosal biopsy is also supported by prospective study from our own department[12] of 112 new cases with Ta or TI exophytic transitional cell cancer who had quadrant mucosal biopsy at the time of the initial assessment cystoscopy. Patients with one or more abnormal biopsies (dysplasia or carcinoma *in situ*) were shown to have a significantly ($p < 0.01$) higher probability of recurrence (Figure 1). In all cases the only treatment was endoscopic resection or cystodiathermy of the

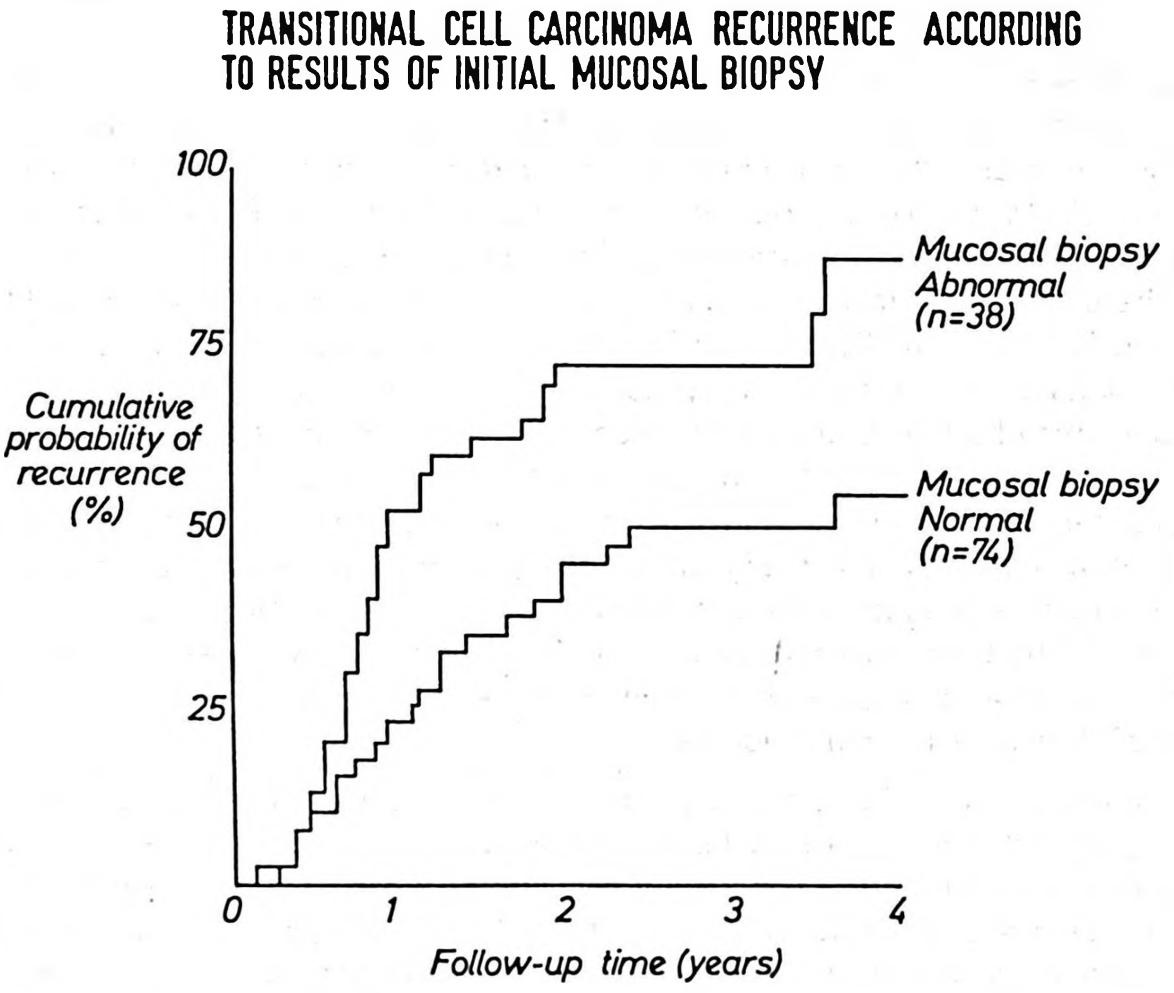

Figure 1.

Transitional cell carcinoma recurrence according to results of initial mucosal biopsy. Life table analysis of 112 patients with superficial tumor who had quadrant mucosal biopsy at the time of their initial assessment (Data from Department of Urology, Western General Hospital).

initial tumor. Further prospective studies are underway (Medical Research Council 1981). The need for assessment of the mucosa cases with superficial tumor has until recently been academic as few urologists would have proposed cystectomy in cases of Ta/Tl tumor. The advent of effective intravesical chemotherapy has, however, changed this. Adriamycin and mitomycin C have been shown to be highly effective in reducing exophytic and *in situ* lesions, and the use of these agents offers the prospect of improved prognosis in high risk cases if such high risk cases could be defined. The assessment of the apparently normal mucosa, identification of high risk patients and treatment with effective intravesical agents is perhaps the brightest current hope in urological oncology and could have as great an impact as chemotherapy for testicular teratoma.

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DISCUSSION

Kırkalı: Instead of taking biopsies from the bladder mucosa, why not wash out the bladder with methylene blue and take biopsies from the stained areas?

Hargreave: That's a technique we haven't tried, but I do agree that if you have a reliable technique to pick up the areas that look bad, I think it is perhaps worthwhile;

and to my mind one of the most interesting ways of looking at the problem is with alterations in light and the hematoporphyrin story because there is a possibility there for both diagnosis and treatment; but as yet the scheme is not practical. The last word I heard on this was when they showed a slide of a room about this size, filled up with apparatus to produce the right colored light. It was obviously a long way from being practical in the United Kingdom anyhow.

Hussien: The rate of loss of antigenicty and recurrence are higher in Grade II than in Grade III, How can you explain that?

Tuncer: Yes, the loss of antigenicity was obvious in Grade II and also in Grade III. The relation between the loss of antigenicity and the grade of tumor was significant between Grade I and Grade II and between Grade I and Grade III. We couldn't find any significant relation between Grade II and Grade III. It was obvious in Grade II and also obvious in Grade III patients. There were more patients with Grade II than with Grade III tumors.

Hussien: What's the explanation, since it was about 100% in Grade II while it was 66% in Grade III?

Tuncer: Actually, when we look at the positive staining of the tumor, there is non-uniform distribution of tumors in the neoplastic tissue, and this may explain the positive stain in different grades of tumors.

Hussien: Is there any relation between the mucosal changes and the multiplicity of the tumor itself within the same patient?

Ruacan: In this small group of patients - 25 in all - there were no multiple tumors, they were all single tumors. So I can't answer that.

Hargreave: Yes, I think there is some relationship. If I remember rightly, multiple tumors are more likely to have dysplasia. That's what's given in the literature. But, one of the problems, when you have this type of information, is to say what the relative importance of each of the various factors is. We didn't have many multiple tumors, and when we did a Cox's multivariate analysis, the mucosal abnormality was adding information that we were not getting by smearing because of the multiplicity of the tumors; so the fact that you've got a multiplicity of tumors is a prognostic factor, but if you knew about the abnormal mucosa as well, that was adding information.

Hussien: Do you think the degree of the distention of the bladder during the performance of the biopsy has any effect on the results, and do you think there should be a standardized level of distention before taking a biopsy?

Hargreave: I can't answer that in any sort of scientific way except to say that in the series I was concerned with, I took most of the biopsies myself and my habit is to

use normal saline to urethroscope and fill the bladder, and I don't fill the bladder to full distention. I fill it till it's partially distended because actually I don't like to dig the little forceps in and try and push right through the bladder; in fact it's much easier to take the biopsies with the bladder not too well distended, so you can take a little nip of mucosa which is all I was trying to do. I didn't actually want to get muscle in my mucosal biopsies, so all I can say is that throughout this series, the conditions under which the biopsies were taken were fairly standard; not so the biopsy changes. So it may be that I distended those with positive biopsies more than the ones with negative biopsies but I don't think so.

Wickham: I just want to ask from the practical point of view, having determined this marker of incipient recurrence, how is it going to influence your treatment regime?

Hargreave: Well, I don't think it is and I was trying to make that point at the end, that I think we have something quite simple as a mark of recurrence, and at the moment we are engaged, worldwide, in trials of intravesical chemotherapy. And I think it would be reasonable, therefore — though I know this is contested in some quarters — to include a biopsy protocol when we are evaluating intravesical chemotherapy as part of a scientific evaluation. But for the day to day clinical management of transitional carcinoma of the bladder I do not think that the extra work and expense for the hospital is justified.

Smith: You had 57 patients with abnormal findings out of 112. How many actually had carcinoma *in situ*?

Hargreave: Oh, very few. Perhaps three percent. You can in fact altogether forget carcinoma *in situ* in your analysis; the vast majority of the prediction is from dysplasia. I should also say that we have a weekly bladder cancer meeting at which these slides are projected by our pathologist, and we have a good in-house criticism by our three pathologists. It's the agreed findings of this meeting that we record. So I think there's a fair amount of in-house consistency, but as you well know if you were to send these slides off to another pathologist in another place you'd get answers back saying that there was in fact no dysplasia at all. So that's also a problem. This is why I really do think that this is still an aspect of practice that is in the research phase only.

Ruacan: I think this is a very interesting point, and very significant in studies of this type. There is no internationally accepted methodology, and different people have different views regarding biopsies, and their pathological classification, infact, the system is really quite controversial. Some people sub-group dysplasias according to mild, moderate and severe; some give them numbers; certain pathologists, for example those in the Scandinavian countries, consider Grade III dysplasia as equal to carcinoma *in situ;* some are at a loss to differentiate between severe dysplasia

and carcinoma *in situ.* I think the problem is more complex in the urothelium than in the uterine cervix, the squamous epithelium and elsewhere, where criteria for dysplasia and carcinoma *in situ* are much better elucidated. Usually, for instance in the uterine cervix and with squamous epithelium and squamous mucosa, carcinoma *in situ* is a long and tedius process taking approximately 10 years to grow into invasive carcinoma, whereas in the urothelium it appears that recurrences are taking place at a much more rapid pace and are being seen in a much shorter time. I don't know if this reflects a biological property of the tissue itself, or if there are other factors of carcinogenesis.

Chisholm: Can I comment a bit? You say there is no system of classification, but actually some people assert quite strongly that there is. The other month I heard someone making a classification of Grade I, Grade II and Grade III carcinoma *in situ,* which I certainly do not feel happy about. But I think the point is quite an interesting one to think about; at the moment, carcinoma *in situ* by definition is a Grade III tumor. So anything less has to be grouped as severe dysplasia. I'm certain, however, and I'll mention it again in my next paper, that there are not a lot of important differences between severe dysplasia and carcinoma *in situ.* As far as I'm concerned, I would bracket them together.

Hargreave: Can I come back slightly on that. It seems that severe dysplasia or Grade I carcinoma *in situ,* will predict papillary recurrence but the rate of prediction is not really important enough to alter our management. The only thing that actually matters is real carcinoma *in situ* which has a greater predictive base of recurrence leading to death.

Chisholm: Well, I think if you can show that, that's fine. The problem is showing it.

Hargreave: And that's why, in this series, we are simply continuing to follow up these patients and we are not acting on our mucosal biopsy findings; they are having standard treatment, which is just endoscopic resection of recurrences.

Smith: Another point, in relation to carcinoma *in situ* and the uterine cervix. We haven't so far considered this carcinoma *in situ* as asymptomatic and in the presence of a patient with a known tumor, but perhaps we ought to do so.

Hargreave: I think we have to make that point very clear; there was no primary carcinoma *in situ* in the series I reported; these were all cases with an exophytic superficial TA TI lesion, with or without associated abnormalities.

Chisholm: Can I come back to Doctor Kırkalı's point that there is a flaw in all of this. A random biopsy is just a fraction of the urothelium. I don't know what percent it might be, 0.001 of the urothelium perhaps. And I think that what we want if someone can get round to it, is an easy way of reliably showing a mucosal dysplasia. The trouble with the present methods, and the trouble I have to say with the red-cell

isoantigens, is that the trend is there but it's not complete. That's the point; it's got to be complete to persuade you to use it clinically. We're back to what I said earlier: bad tumors do badly. There are some quite good ones, though, that do badly too, and until we can pick those out, I think we're quite a long way off sorting this out.

Hargreave: In our series of those who have actually had red-cell antigens done — they've not all had it done yet, but many of them have — the red-cell antigens are not actually predicting recurrence, at least not according to the follow-up that we have so far.

Wickham: Could someone tell me what the practical application of all this is amounting to? Is it going to alter your treatment in anyway? Are you ever going to say to a patient with a severe dysplasia, you might as well have your bladder out right now because in 10 years time you're going to get a nasty carcinoma.

Hargreave: No, but I might say to him, "You come into my ward for two weeks for daily mytomycin instillations because that will alter your bladder mucosa and mean that in the future you will not have this risk. Now obviously, at the moment, we are nowhere near being able to say this, but we do at least have intravesical agents that obviously have a powerful effect on exophytic tumors.

Wickham: Yes, but nothing on *in situ* tumors.

Hargreave: Well, it's not proven yet.