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Author(s)	Tock, E.P.C; Foo, K.T; Tung, K.H; Tan, E.C
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## Carcinoma of The Urinary Bladder in Singapore

E. P. C. Tock,\* K. T. Foo<sup>+</sup>, K. H. Tung<sup>+</sup> and E. C. Tan<sup>+</sup>

*Department of Pathology\* and the Department of Surgery<sup>+</sup>  
National University of Singapore*

### INTRODUCTION

Carcinoma of the urinary bladder is relatively common in Singapore, being the tenth commonest cancer in the male population (Singapore Cancer Registry 1985) The present study examines the pattern of this malignant disease in the Singapore population, in terms of clinical presentation, pathology, and management. It is based on an analysis of cases of transitional cell carcinoma of the urinary bladder as seen in the Department of Surgery, National University of Singapore, over a period of 12 years, from 1973 to 1984 inclusive. The study is divided into two parts ; the first part deals with invasive carcinoma of the urinary bladder, while the second part is concerned with intra-epithelial carcinoma or carcinoma-in-situ.

### PART I : INVASIVE CARCINOMA OF THE URINARY BLADDER MATERIAL AND METHODS

A retrospective study was made of 73 cases of invasive carcinoma of the urinary bladder seen at the Department of Surgery of the National University of Singapore during the period 1973 to 1978. The cases were identified from the records of the Singapore Cancer Registry at the Department of Pathology and the clinical data were derived from the patients' case records. The authors have also been analyzing all cases of bladder carcinoma seen after 1978, but the additional data obtained do not throw further light on the subject than what is presented in this paper.

### RESULTS AND DISCUSSION

#### *Age, Sex and Racial Distribution*

Of the 73 patients reviewed, 60 were males and 13 females, giving a male preponderance of 4.6 to 1. The male to female ratio reported in the literature varies from 2.3 : 1 (Anderson, 1973) to 5 : 1 (Westcott, 1966) This male preponderance has been attributed to urothelial carcinogens such as through cigarette smoking and occupational exposure. In Singapore, while there is a much higher incidence of smoking among males than females, there is no known occupation involving exposure to known urothelial carcinogens. The use of beta-naphthylamine as an antioxidant in tyre manufacturing has been banned for the last two decades or so. The dyeing industry, seen largely in the batik making, does not utilise any known carcinogenic dyes. Sixty-four of the 73 patients (or 87.7%) were Chinese. This is consistent with the predominance of Chinese in the Singapore population and therefore does not indicate any ethnic predilection. The majority of the patients (63 out of 73, or 86.3%) were in the fifth, sixth and seventh decades of life. Only 2 patients, both males, were below 40 years of age.

#### *Clinical Presentation*

Haematuria was by far the commonest presenting symptom, occurring in about 85% of patients. Haematuria occurs either as the sole complaint or in conjunction with cystitis and/or outflow obstruction. Hendry and Bloom (1976) have also recorded the overwhelming frequency of haematuria as a

presenting symptom. One patient had a palpable suprapubic mass. Other symptoms were mainly backache and loin pain. The duration of haematuria correlated positively with the stage of the disease found at operation ; patients presenting with T<sub>3</sub> and T<sub>4</sub> tumours had a long history of haematuria (for months).

#### *Intravenous Urogram Findings*

An analysis was made of the available intravenous urograms (IVU) of 61 patients. As many as 15 patients (or 24.6%) had a normal VU. Sixteen patients (or 26.2%) had evidence of unilateral or bilateral ureteric obstruction. In 35 patients (or 57.4%) the IVU showed a filling defect. In 26 patients (or 42.6%), the tumour was not outlined. Thus, a normal bladder outline did not exclude a bladder tumour.

#### *Clinical Staging*

The inaccuracy of clinical staging is well known. Hence, histopathological examination of biopsy and resection specimens was used to verify or modify the clinical staging. Thirty-five cases (or 47.9%) were T<sub>1</sub> tumours. T<sub>2</sub> tumours accounted for 11 cases (or 15.0%), T<sub>3</sub> for 16 cases (or 21.9%), while 6 cases (or 8.3%) were staged T<sub>4</sub>.

#### *Clinical Staging and Pathological Grading*

A correlation was observed between the clinical stage and the pathological grade ; T<sub>1</sub> tumours were usually Grade I or II (well or moderately differentiated), while T<sub>3</sub> and T<sub>4</sub> tumours were generally Grade III (poorly differentiated).

#### *Number of Tumours*

The majority, 52 out of 73 (or 71.3%), of the patients had single tumours ; 15 (or 20.5%) had multiple tumours (less than 6), while 3 patients (or 2.19%) presented with papillomatosis.

#### *Site of Tumours*

The lateral walls were the most common sites, with 51 patients (or 69.8%) presenting with lateral wall tumours, the left and right walls being affected about equally.

#### *Gross Morphology of Tumours*

Forty-two patients (or 57.5%) presented with papillary lesions, 19 patients (or 26%) had solid tumours, while 2 patients (or 2.7%) had ulcerative lesions which represented a late stage of the disease.

#### *Gross Morphology and Clinical Staging*

Papillary tumours were more likely to be early stage, while solid tumours tended to be invasive.

#### *Histological Types of Tumour*

The vast majority, sixty-nine, of the patients (or 94.5%) had transitional cell carcinoma. There were only 2 cases of adenocarcinoma (or 2.7%) ; there were also 2 cases (or 2.7%) of squamous cell carcinoma, one of which occurred in a bladder diverticulum.

#### *Modes of Therapy and Results*

A range of treatment modalities had been employed, varying from cystodiathermy alone to total cystectomy. The series therefore lacked a uniform policy of management. For T<sub>1</sub> tumours, before 1976, treatment was by biopsy and cystodiathermy ; since 1976, transurethral resection became available and was the treatment of choice. This method was also used for T<sub>2</sub> tumours followed by radiotherapy. For T<sub>3</sub> tumours, the recommended treatment was a course of radiotherapy, followed by cystoscopy at 4 to 6 weeks later, and, if there was no response, a total cystectomy was performed. For T<sub>4</sub> tumours, only palliative radiotherapy was administered.

The overall mortality was 46.6% with 34 deaths, of which 22 (or 64.7%) were attributed directly to carcinoma of the bladder. The majority of the patients succumbed within the first two years. Eight patients with T<sub>1</sub> tumours died, but 6 of these died of causes other than bladder carcinoma. The majority of patients with invasive carcinoma died of the malignancy. Carcinoma of the bladder presents with certain specific management problems. The concept of the "urothelium" as a single continuous membrane lining the urinary tract implies that eradication of a tumour in the bladder does not mean eradication of the disease, since urothe-

lial tumours may still develop in other parts of the urinary tract as long as the aetiological factor (s) exists. Also, a problem exists in deciding on the preservation of the bladder. Late tumours are generally treated more radically than early tumours. However, for early stage, low grade lesions, one is confronted with the problem of whether total cystectomy should be performed, bearing in mind that about 15% of T<sub>1</sub> tumours become invasive later on. Nevertheless, because of the good response of some patients to radiotherapy, and the mortality and morbidity attending cystectomy, selectivity should be exercised in performing total cystectomy. For low grade tumours (confined to the lamina propria), the policy adopted is cystoscopic resection. Radiotherapy is given in addition if there is superficial muscle involvement. Multiple small, superficial low grade tumours may be controlled by intravesical cytotoxic therapy. Localised high grade tumours especially near the vault of the bladder may be treated with partial cystectomy. Papillomatosis of the bladder would need total cystectomy. Lastly, because bladder carcinomas tend to be multiple not only in space but also in time, a programme of regular checks for recurrences has to be established; its rationale also has to be convincingly explained to the patient to ensure his compliance for regular follow-up checks. This of course does not apply to late stage disease with poor prognosis regardless of the mode of treatment.

## PART II : CARCINOMA-IN-SITU OF THE URINARY BLADDER

Carcinoma-in-situ of the urinary bladder was first described by Melicow and Hollowelin 1952; however, it was not well recognised as a clinical entity until 1970 when Utz and his co-workers described the plight of the patient with this condition. The diagnosis of carcinoma-in-situ of the bladder is important because of prognostic and therapeutic considerations, since a high proportion of cases develop muscle invasion and become life-threatening. However, not all patients invariably develop invasive disease, and in a significant number of them, the disease may be dormant and run a relatively benign

course (Fridell, 1976; Farrow et al, 1976). This poses problems in management as it is difficult to predict the course of the disease in a particular patient. Nevertheless, with a better understanding of the natural history of the disease, a general outline in its management would be useful in order to avoid undertreatment or overtreatment. This paper serves to increase awareness of carcinoma-in-situ of the bladder in Singapore, and also proposes a general policy in the management of the disease.

## MATERIAL AND METHODS

Transitional cell carcinoma-in-situ of the urinary bladder is defined as intra-epithelial carcinoma occurring in otherwise normal bladder mucosa, in the absence of papillary formation. The degree of differentiation is poor, corresponding to Grade III in the W. H. O. Classification.

For the five-year period from 1980 to 1984, 130 cases of transitional cell carcinoma of the bladder were seen at the Department of Surgery of the National University of Singapore. Eighty-two (or 63%) of the cases were staged as superficial carcinoma (T<sub>1</sub> growths), while 48 (or 37%) were diagnosed as muscle invasive cancer (T<sub>2</sub>, T<sub>3</sub> and T<sub>4</sub> growths). Among the 82 cases of superficial carcinoma, 12 (or 15%) were confirmed histologically to have transitional cell carcinoma-in-situ; all 12 cases were found in association with overt papillary carcinoma either at the same time or at subsequent follow-up cystoscopy. There were no cases of isolated carcinoma-in-situ in this series.

The pathological specimens of all the 12 cases were reviewed by one of the authors (E. P. C. Tock).

## RESULTS AND DISCUSSION

There were 10 males and 2 females, giving a male preponderance ratio of 5 : 1. The ages of the patients ranged from 30 to 73 years with a mean of 57 years. All ethnic groups were affected with no obvious predilection. The majority (10 out of 12 cases) were diagnosed in the past 1½ years. All the patients except one had gross

haematuria. On cystoscopy, carcinoma-in-situ (on correlation with histological confirmation) most commonly appeared as flat areas of hyperaemia, best described as velvety areas, with no papillary lesion. These areas had ill-defined margins and were best appreciated with the bladder about one-third full. Occasionally, carcinoma-in-situ appeared normal on cystoscopy, and random biopsy of such "normal looking" mucosa have shown carcinoma-in-situ in some instances.

Cytological smears of bladder washing in all cases showed malignant cells, including those patients who at the time of cytological examination had no obvious papillary, solid or ulcerative lesions. Our findings illustrate the point that the overt papillary lesion tends to attract more attention than the flat lesion of carcinoma-in-situ and if no biopsy of the latter or cytology is done, the lesion will be missed.

Our current routine practice is to do random biopsies of normal looking mucosa as well, in all cases of bladder tumour.

Once a diagnosis of carcinoma-in-situ has been made, close follow-up of the patient is mandatory, because of the tendency of the lesion to progress to invasion. Management of carcinoma-in-situ of the bladder is problematic because its natural history is not quite well understood and its treatment is still controversial. Utz at the Mayo Clinic has advised that if on initial diagnosis, the patient is symptomatic and the lesion is diffuse involving the trigone and/or prostatic urethra, then total cystectomy should be performed. If the lesion is localised to less than 3 cm in diameter, and the patient is relatively asymptomatic, then intravesical chemotherapy should be given. If after 6 to 9 months of intravesical therapy, there is no improvement, then total cystectomy should be done, if the patient is reasonably fit.

We feel that a period of 6 to 9 months may be too short a time to assess any particular individual with carcinoma-in-situ of the bladder because of its long natural history before it becomes invasive. (Fridell, 1976). Such patients, including those with a diffuse lesion, could be given a trial of chemotherapy. A number of intravesical chemotherapeutic agents are now available such as thiotepa, mitomycin C,

adriamycin, and, more recently, BCG. It appears justifiable to try intravesical treatment with the various agents, at the same time keeping a close watch on the patient. Perhaps conservative management could be continued until such time as all available effective intravesical agents have been exhausted or when there is invasion. With greater awareness of the disease, more cases in future will be diagnosed earlier, and hopefully with early institution of intravesical chemotherapy, progression to muscle invasion can be prevented, and the number of cases requiring cystectomy minimised.

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