

Squamous cell carcinoma of the bladder. a comparison of pathological features and survival outcomes with transitional cell carcinoma of the bladder

Abstract

Objective: To directly compare differences in outcomes and tumour pathology between transitional cell carcinoma of the bladder (TCC) and non-bilharzial squamous cell cancer (NBSCC) of the bladder following radical cystectomy.

Methods: Retrospective analysis of 258 patients undergoing cystectomy by one surgeon. Comparison of primary tumour characteristics and long term outcomes.

Results: SCC fares worse in all measurable outcomes, progression free mortality (PFM), disease specific mortality (DSM) and all cause mortality (ACM).

Conclusion: SCC fare worse due to much greater size of tumour and being locally advanced at presentation. Post surgery SCC has a great percentage of positive surgical margins despite a lower grade than one would expect for such aggressive disease.

Keywords: squamous carcinoma bladder, radical cystectomy, outcomes

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Abbreviations: TCC, cell carcinoma of the bladder; NBSCC, non-bilharzial squamous cell cancer; PFM, progression free mortality; DSM, disease specific mortality; ACM, all cause mortality

Introduction

Bladder cancer is the most common cancer of the urinary tract¹ mostly consisting of TCC. 2-5% are SCC hence less is known about this subtype. SCC is formed of two varieties, the most common worldwide is bilharzia related SCC and the lower incidence type of NBSCC² which is more common in the west and the USA and forms the basis of this article. NBSCC is usually associated with long term catheter use and spinal cord injury in addition to smoking.^{3,4} They are generally diagnosed at an advanced stage 93% of cases,⁸ and this appears to be the reason why they are associated with a poor prognosis and an all cause mortality (ACM) of 7-50%^{3,5} 37%⁶ 48%⁷ 2%.⁸ The grade is less important to prognosis and NBSCC is associated with a greater incidence of intermediate and low grade tumours. Lymph node status and vascular density also influence aggressiveness. Treatment has not been definitively ascertained.

It is treated with radical cystectomy as the gold standard. The use of other modalities such as radiotherapy, chemotherapy and immunotherapy have not been well established either alone or in combination.⁹

We show in our series that there are many unusual features of this tumour. We directly compare the two types of tumour and their outcomes following radical cystectomy.

Methods

A search of PubMed database was performed using search terms of radical cystectomy, squamous cell carcinoma bladder and outcomes. 28 references were sourced.

Study population was 258 patients who underwent radical cystectomy performed by one surgeon only and were followed over 18 years. Patient information was accessed from ICE (clinical information), IQutopia (operative information) and carestream radiology (staging). 230 had transitional cell cancer and 16 had squamous cell cancer on final histology.

A dedicated bladder pathologist reported the cases. Statistical analysis was calculated using Medcalc and Excel statistical packages. Kaplan Meier curves are generated and P values estimated for significant differences between the two cohorts. Patient demographics and tumour characteristics clinical, pathological and radiological are compared and statistical tests performed.

Tumour volume is rarely documented by pathologists despite being an important prognostic indicator. Usually on length and width of tumour are reported. In order to approximate the tumour depth dimension we proposed using half the width. Thus we approximated the volume using the ellipsoid formula of $\pi/2 \times \text{length} \times \text{width}$ and assuming depth to be 0.5 of width. The error introduced is not ideal but it is systematic and approximates the true volume and any significant differences will still be revealed regardless if they are under or overestimated.

Results & discussion

Table 1 Patient, tumour features and outcomes.

Epidemiology

In the west NBSCC is the predominant subtype with a poor outcome.² SCC is quoted as accounting for only 1% of bladder cancer in UK. Our series is composed of 6% NBSCC. Patients are usually diagnosed in the seventh decade with a slight male predominance.¹⁰ We have noted a number of differences between the two categories

of SCC and TCC. Our series showed a predominance of women 69% with SCC which is contrary to most bladder cancer series with 19% TCC being women. Both cohorts are of a similar age 67-68 years old. NBSCC is associated with neurogenic bladder and chronic irritation from catheter use, BOO and urine stasis.^{3,11} Smoking is a well recognised risk factor for both TCC and SCC of the bladder.

Bladder irritation, UTI and chronic inflammation all contribute to an environment generating cytokines and growth factors predisposing to cell proliferation, migration, angiogenesis and inhibition of apoptosis, in turn leading to squamous metaplasia, dysplasia and cancer.^{12,13,14} The relation with HPV is controversial and unclear.¹⁵

Table 1 Patient, tumour features and outcomes

	16 Squamous cell	230 Transition cell	P value fishers and t
Private	3	32	0.7
Male/female	11-May	185/45	0.03
Age	67	68	0.58
Neobladder	2	51	0.37
Grade High	8	213	0.0001
Intermediate	6	17	0.0021
Low	2	0	0.0045
Tumour volume cc	101	14	0.019
Positive surgical margins	6/16 (38%)	21/230 (9%)	0.0052
Localised/locally advanced	3/13 (19%)	140/90 (61%)	0.0006
CIS	6	105	0.45
Node positive patients	4	51	1
Number of nodes positive (total number of nodes)	13	128	
Node harvest	214	2299	
Node density	0.06	0.055	0.75
Extracapsular extension	2	22	
Proportion of ECE	2/13 = 0.15	22/128 = 0.17	1
Prostate cancer	2/5 =0.4	83/185 = 0.45	0.69
Complications	4	59	1
Additional treatment (neo-adjuvant, adjuvant chemotherapy, radiotherapy)	2	44	0.76
Progression free survival at 5 years	0.63	0.76	0.046
Disease specific survival at 5 years	0.5	0.71	0.0037
All cause survival at 5 years	0.13	0.61	0.0001
Number of disease specific deaths	8 (50%)	80 (35%)	0.31
Number of all cause deaths	14 (88%)	113 (49%)	0.01

Clinical and pathological features

Haematuria is the most common presentation although storage symptoms can occur. Along with pelvic pain, back pain and hydronephrosis. SCC is an epithelial neoplasm showing squamous pearls, intercellular bridges and keratohyalin granules. Pure SCC does not contain urothelial elements.¹⁶

Cystoscopically the tumour is large and solitary with associated leukoplakia and can be anywhere within the bladder. They are rarely superficial (Ta/T1). T3 invasion into perivesical fat is the most common stage representing 60% of the cases.^{18,25} Our series had 81% locally advanced T3 and T4.

The SEER database also showed the grade to have significant amounts of intermediate and low grade tumours.²⁵ This unusual feature was replicated with our experience showing 50% with non high grade SCC as opposed to only 7% with TCC. 8 cases were low (2 cases) or intermediate (6 cases) grade SCC.

SCC also has low rates of lymphovascular invasion and nodal metastasis only 18%.²⁶ There was no significant difference in node positivity or extracapsular extension of tumour within the nodes. There was no difference in the rates of carcinoma in situ between the two cohorts. Neither was there a significant difference in rates of coincidental prostate cancer, neo-bladder, complications or additional treatments.

Prognostic and survival outcomes

Prognosis is related to stage, grade, LVI, nodal involvement and insurance status.^{7,8,26,22} Stage 3 and 4 disease progression is more rapid than TCC. The SEER data shows both a worse all cause and disease specific mortality for SCC.²⁷ Our findings strongly support the idea of worse outcomes with SCC at five years and indeed at longer follow up. Other studies have shown overall survival is equivalent according to a Canadian study.²⁴ The cause appears to be the relatively massive size of the NBSCC. Our tumour mass is 101cc compared to a TCC mass of only 14cc. This very large volume eclipses all other types of tumour volumes.^{24,25} This in turn leads to an advanced stage with only 19% localised (T1/T2) to bladder in NBSCC compared with 61% localised in TCC. Similarly the positive surgical margin rate is 38% in NBSCC compared to only 9% in TCC.

The worse prognosis is due to the more advanced stage and the presence of positive margins which outweigh the protective effect of lower grade. Both long-term survivors in SCC cohort had high grade tumours. Interestingly, we do not see any greater lymph node involvement. These are the probable reasons for the poorer prognosis of NBSCC. 90% of mortality is related to local recurrence at either urethral or ureteric anastomosis. Distant metastasis is uncommon.² Death is due to obstruction and renal failure.²⁶ Molecular analysis may also contribute and Fibroblast growth factor 2 overexpression and cyclooxygenase 2 alterations are indeed associated with worse outcomes.¹⁵ There is little in the way of high quality level 1 prospective studies regarding treatment options. Radical cystectomy, lymphadenectomy and urinary diversion is the gold standard.^{2,18,27} A five year survival of 48% has been reported⁷ but subsequent analysis showed it to be lower. Far lower survival has been reported elsewhere.⁸ Most series report on bilharzial squamous cancer and studies solely reporting non bilharzial squamous cancer are in the minority.²⁸

Tumour volume

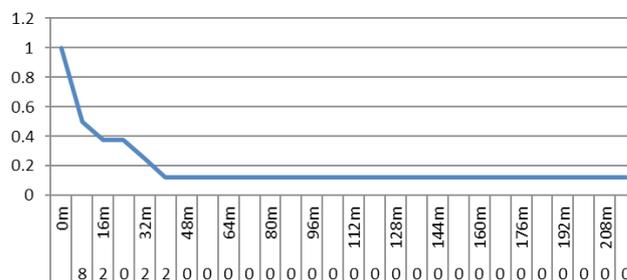
The tumour presents as bulky locally advanced disease and is unsuitable for partial cystectomy. The tumour is very large and significantly larger with a mean volume of 101cc compared to 14cc with TCC and other histologies including sarcoma²⁵ and smallcell cancer.²⁴ It may be that we have underestimated or overestimated the tumour volume using our ellipsoid method, but the difference still remains and is extremely significant statistically and clinically. There was, however, no significant difference between tumour volume of high grade SCC (101cc) compared to medium and low grade SCC (111cc). Only 19% of SCC were localised (T1 or T2) compared to 61% for TCC. 81% of SCC were locally advanced (T3 or T4).

The worse prognosis is due to the greater stage and the presence of positive margins which outweigh the protective effect of lower grade. Both long-term survivors in SCC cohort had high grade tumours. 38% of SCC had positive surgical margins compared to only 9% of TCC. Interestingly, we do not see any greater lymph node involvement.

The effects of greater stage and positive margins translate to worse outcomes in all 3 parameters of progression free mortality, disease specific and all cause mortalities. We see an earlier tendency to progression (Graph 1 40% at 5 years local recurrence or distant metastasis) for SCC compared to only 24% for TCC. There is a higher disease specific mortality of 50% (Graph 2) for SCC compared to only 29% for TCC at 5 years. However, there is a far higher all cause mortality of 81% at 5 years (Graph 3) with SCC compared to 39% for TCC. Although the figures are given for 5 years of follow up, the patients were followed up for a total of 160 months or 13 years with no significant change beyond the 5 year period (Graph 4).

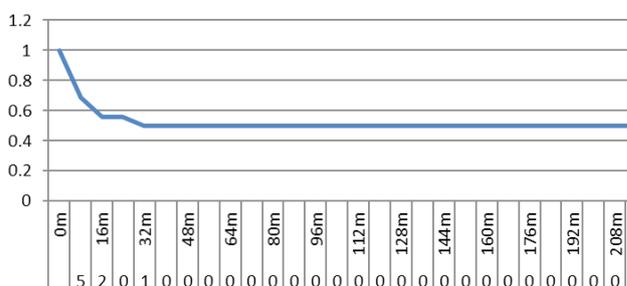
Graph 1

all cause specific mortality over 18 years for SCC



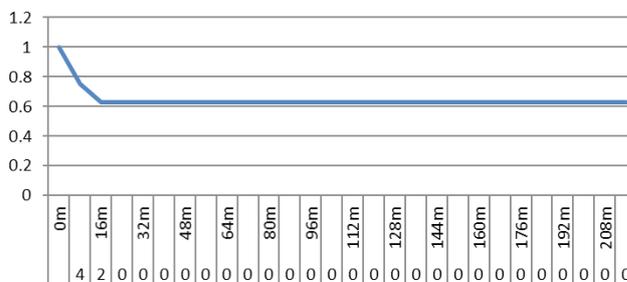
Graph 2

disease specific mortality over 18 years for SCC



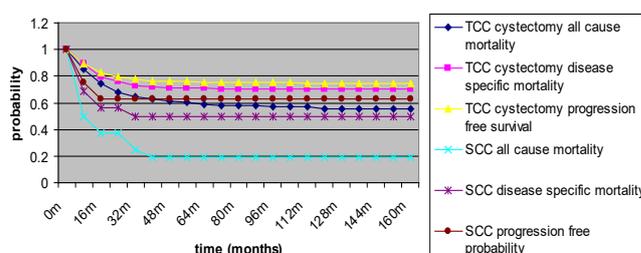
Graph 3

probability of progression free survival over 18 years for SCC



Graph 4

squamous v transitional cell cystectomy



Prevention

Early detection is key and avoidance of chronic infection, long term catheters and smoking should be avoided if at all possible.

Criticisms

We did not look at LVI, infection history, cord injury. Tumour volume depth was approximated. However the same systematic error is maintained throughout, so the comparison remains pertinent. This study has a relatively small number of patients but the differences were extremely significant and therefore of some value.

Strengths

The same surgeon and pathologist were used throughout and this removes potential subjective biases. One geographical area eliminates national differences that may obfuscate. The use of tumour volume is highlighted as a useful parameter in prognosis and behaviour clinically. This has not been emphasised before and its inclusion is useful for prognosis, in addition the estimation of volume is acceptable even if only a length and width are given.

Conclusion

The patients with NBSCC have very large tumours that are significantly locally advanced with positive surgical margins. The tumour volumes are of a similar size amongst the range of grades in SCC. The SCC have a much greater proportion of low and moderate grade tumours. There is a greater progression free, disease specific and all cause mortality for SCC. Low and medium grade SCC does not confer a survival advantage, the effect of great volume, advanced stage and PSM being more powerful determinants of prognosis. It may be that advances in radiotherapy, neo-adjuvant and adjuvant chemotherapy along with immune treatments may improve prognosis.

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

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