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Risk factors for development of primary bladder squamous cell carcinoma

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ABSTRACT

INTRODUCTION The aim of this study was to investigate the prevalence of risk factors for primary squamous cell carcinoma (SCC) of the bladder.

MATERIALS A total of 90 cases of primary SCC of the bladder were identified through multicentre analysis. Patient demographics, stage and grade of cancer at presentation, management and outcomes were recorded. The presence of known risk factors (catheter use, neuropathic bladder, smoking history, recurrent urinary tract infection and bladder stones) was also documented.

RESULTS Over half of the patients had at least one identifiable risk factor for the development of primary bladder SCC: 13.9% of patients had a history of catheter use (clean intermittent self-catheterisation [CISC] in 11.1%), 10.0% of patients had a neuropathic bladder, 27.8% were smokers or ex-smokers and 20.0% had a documented history of recurrent urinary tract infection. Statistical analysis of the results showed no association between risk factors and grade of tumour at presentation.

CONCLUSIONS These data further support the association between primary bladder SCC and several of the well documented risk factors for its development. Chronic use of CISC may confer a greater risk for development of SCC than thought previously. Further evidence of the role of CISC in primary SCC is required to justify routine screening and to determine exactly when surveillance of the bladder should begin for this group of patients.

KEYWORDS

Primary – Bladder – Squamous cell carcinoma – Clean intermittent self-catheterisation

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Primary squamous cell carcinoma (SCC) remains a relatively infrequent cause of bladder malignancy in the Western world, accounting for less than 5% of all cases of bladder cancer.[1] While the predominant risk factor in the Middle East, Southeast Asia and South America is chronic infection with schistosomiasis, risk factors in Western countries are those associated with repeated urothelial injury and the induction of keratinising squamous metaplasia such as recurrent urinary tract infection (UTI), radiation exposure, smoking, spinal cord injury (SCI) with neurogenic bladder and the presence of foreign bodies (eg catheters or bladder stones).[2]

Although risk factors and the role of bladder management in the development of SCC has been studied in the SCI population, less information is available regarding the relationship of bladder management and SCC in the general population. We present an analysis of the largest series of cases of primary SCC to date with the aim of identifying salient risk factors. The role of increased or formalised surveillance in high risk patients is also discussed.

In general, primary bladder SCC is marginally more common in males than in females (with a ratio of 1.25:1) and it tends to present in the seventh decade of life.[3] The most commonly reported presenting feature is haematuria (63–100%) while other symptoms include dysuria, recurrent UTI and suprapubic pain.[1,4] Cystoscopy and biopsy is the preferred method of confirming a histological diagnosis, and either computed tomography or magnetic resonance imaging is employed for radiological staging.[5]

Presentation of primary SCC usually occurs at an advanced stage of the disease process, the majority (80%) having developed muscle invasive disease (stage T3 or higher).[6] Diffuse metastatic lymphadenopathy is less common than in cases of urothelial carcinoma, with distant metastases occurring in 8–10%.[1] Radical cystectomy combined with lymph node dissection is the mainstay of treatment for those patients with clinically local disease[7] but outcomes are generally poor. Five-year survival rates are reported as 33–48%.[8] Surgical intervention is the preferred management as there is currently a lack of evidence to

support the efficacy of chemotherapy/radiotherapy in treating primary bladder SCC and tumour response to these treatment modalities is frequently suboptimal.[9] There are some small studies that have suggested there may be a benefit from neoadjuvant irradiation.[10]

Approximately 25% of cases are too advanced for surgery at presentation.[6] For those patients presenting with advanced disease, treatment options include radiotherapy or palliative resection.

Methods

A multicentre retrospective analysis of patients with a diagnosis of bladder SCC was conducted using data from a ten-year period (January 2003 – January 2013). Cases were identified using a histology database that permitted searches of data based on histopathological diagnosis coding from the two East of England cancer centres: Addenbrooke's Hospital in Cambridge and the Norfolk and Norwich University Hospital. Overall, 283 cases of bladder SCC were isolated in this way. Histology was reviewed in each case and cases were excluded from analysis if there was a diagnosis of secondary SCC, urothelial cell cancer with squamous differentiation or primary SCC of any organ other than the bladder. This process identified 90 cases of primary bladder SCC for analysis.

All case notes were reviewed to identify patient demographics, stage and grade of cancer at presentation, management and outcomes. Risk factors were also recorded, including type and duration of catheter use (indwelling catheter [IDC] vs clean intermittent self-catheterisation [CISC]), presence of a neuropathic bladder, smoking history, recurrent UTI and bladder stones.

Results

Of the 90 cases of primary bladder SCC reviewed, 38 patients (42.2%) were women and 52 (57.8%) were men. The median age at diagnosis was 72 years (range: 36–93 years).

Presenting symptoms

Haematuria was recorded in 54 patients (60.0%), with visible haematuria in 48 (88.9%). Other presentations included recurrent UTI (n=16, 17.8%), abdominal pain (n=9, 10.0%), lower urinary tract symptoms (n=6, 6.7%), weight loss (n=3, 3.3%), acute kidney injury (n=3, 3.3%) and hypercalcaemia (n=1, 1.1%). The diagnosis of primary bladder SCC was an incidental finding in 10 patients (11.1%). For those in whom it was not an incidental finding, the median time from date of onset of initial presenting symptoms to cystoscopy was 37 days (range: 5–390 days).

Extent of disease

At the time of first diagnosis, nine patients (10.0%) were found to already have metastatic disease. The metastases were located in the lung in four cases (44.4%), the bone in three cases (33.3%) and the liver in three cases (33.3%). Overall, four patients (4.4%) had evidence of involved lymph nodes on initial imaging.

Histological staging

The majority of patients had muscle invasive disease at the time of presentation (n=78, 86.7%). Table 1 shows how histological stage and grade were distributed, and nodal status/clinical staging at diagnosis is documented in Table 2.

Management

In total, 34 patients (37.8%) were managed with a radical cystectomy with curative intent. In 39 cases (43.3%), patients were treated with local resection or debulking. Table 3 summarises the surgical and medical management of patients.

Risk factors

Twelve patients (13.3%) had a history of catheter use: CISC in ten (11.1%) and IDC in two (2.2%). IDC use in both cases was as long-term management for bladder outflow obstruction and catheters had been in situ for a minimum of four years.

CISC was recorded for a median duration of 10 years (range: 3–39 years). It was attributable to SCI in four patients (40.0%), multiple sclerosis in two patients (20.0%), urethral stricture disease in one patient (10.0%), spina bifida in one patient (10.0%) and postoperative voiding problems following an aortic aneurysm repair in one patient (10.0%). In one case, the reason for CISC was unknown.

Table 1 Grade and stage of bladder squamous cell carcinoma at presentation

T stage	Grade 1	Grade 2	Grade 3	Grade unknown or N/A	Total
pTis				1 (1.1%)	**1 (1.1%)**
pTa		1 (1.1%)			**1 (1.1%)**
pT1		5 (5.6%)	5 (5.6%)		**10 (11.1%)**
pT2	2 (2.2%)	16 (17.8%)	23 (25.6%)	1 (1.1%)	**42 (46.7%)**
pT3	3 (3.3%)	9 (10.0%)	14 (15.6%)		**26 (28.9%)**
pT4		2 (2.2%)	8 (8.9%)		**10 (11.1%)**
Total	**5 (5.6%)**	**33 (36.7%)**	**50 (55.6%)**	**2 (2.2%)**	**90 (100%)**

Table 2 Nodal status (clinical staging) at the time of diagnosis of bladder squamous cell carcinoma

Nodal status	*n*
N0	30 (33.3%)
N1	7 (7.8%)
N2	3 (3.3%)
Nx	40 (44.4%)

Table 3 Management of patients with bladder squamous cell carcinoma

Cystectomy	*Radical cystectomy alone*	*Radical cystectomy + chemotherapy*	*Partial cystectomy*	*Palliative cystectomy + radiotherapy*
	34 (37.8%)	5 (5.6%)	1 (1.1%)	3 (3.3%)
Local treatment	*Transurethral resection*	*Open excision*	*Local resection + radiotherapy*	*Local resection + chemotherapy*
	27 (30.0%)	3 (3.3%)	7 (7.8%)	1 (1.1%)
Palliative	*Chemo/radiotherapy*	*Radiotherapy*		
	1 (1.1%)	4 (4.4%)		

Overall, nine patents (10.0%) had a neuropathic bladder. Two of these (2.2%) were able to void spontaneously, with no documented history of catheter use (CISC or IDC).

Twenty-five patients (27.8%) had either a current or past history of smoking while eighteen (20.0%) had a documented history of recurrent UTI. Three patients (3.3%) had a history of bladder stones and three (3.3%) had a diverticulum associated with the tumour.

Over half of the patients (n=48, 53.3%) had at least one identifiable risk factor for primary SCC, with a fifth (n=19, 21.1%) having two or more risk factors in combination. The numbers of patients with risk factors for bladder SCC are summarised in Table 4.

Cases were further analysed to investigate the relationship between individual risk factors and grade of tumour to elucidate whether a particular risk factor was associated with a more aggressive malignancy. Cases were analysed to determine numbers of high grade (grade 3) versus lower grade tumours (grades 1 or 2) for each risk factor group using a chi-squared test. The numbers of grade 3 tumours were not significantly higher for any of the risk factor groups (smoking, recurrent UTI, neuropathic bladder) compared with the cases with no risk factors.

Table 4 Patient risk factors associated with bladder squamous cell carcinoma

Risk factor	*n*
Smoking history	25 (27.8%)
Recurrent urinary tract infection	18 (20.0%)
Catheter use	12 (13.3%)
Intermittent self-catheterisation	10 (11.1%)
Indwelling catheter	2 (2.2%)
Neuropathic bladder	9 (10.0%)
Bladder stones	3 (3.3%)
Bladder diverticulum	3 (3.3%)

Discussion

Foreign bodies

Long-term IDCs have been identified as a risk factor for the development of bladder cancer since 1985 when Locke *et al* described malignancy secondary to bladder SCC in 8% of patients who had an IDC in situ for more than ten years.[11] The exact mechanism of oncogenesis remains debateable. However, chronic mechanical irritation and increased epithelial proliferation caused by the catheter balloon are thought to be responsible for the histological changes observed in patients with chronic IDC.[12] In a prospective study from 1999 of 208 patients undergoing surveillance biopsies, Delnay *et al* described an incidence of SCC of 4.8% among those with an IDC for a neuropathic bladder in situ for more than 8.5 years.[12]

More recently, reports in the literature have identified CISC as a potential risk factor for the development of primary bladder SCC.[2,13–16] CISC has been used widely since the 1970s for patients with lower urinary tract dysfunction to avoid surgery or IDCs. Although it was previously thought to minimise histological changes in the bladder compared with IDC use,[17] it has subsequently been hypothesised that CISC promotes progression to SCC through a combination of direct catheter trauma, persistent bacteriuria and keratinising squamous metaplasia.[2]

Finally, another frequent hypothesis is that longstanding bladder stones have a role in the development of primary bladder SCC.[18] As with the mechanisms described above, the chronic mucosal injury and inflammation may facilitate progression to SCC. This is supported by epidemiological studies.[19]

Chemical irritation

Epidemiological data have demonstrated that smoking is a potent risk factor for the development of SCC, with a relative risk of 6.1 for smokers of more than 40 cigarettes per day.[20] The risk of developing SCC related to smoking has been found to be higher than that for other non-transitional cell carcinomas.[21]

Laboratory studies investigating the molecular basis for bladder cancer have shown that exposure to tobacco smoke increases rates of epigenetic methylation of promoter genes and inactivation of tumour suppressor genes, resulting in poorer outcomes.[22] Chromosome 9 has been identified as an important molecular target for damage caused by components of tobacco smoke, with mutations more common in smokers than in non-smokers.[23] Additionally, while smoking

is a risk factor for all genetic subtypes of bladder cancer, it has been suggested that there is a strong association between tobacco smoke and alterations in p53 and retinoblastoma protein tumour suppressor pathways, resulting in more invasive tumours.[25] Less commonly, SCC has been reported in isolated cases following chemotherapy with cyclophosphamide[24] and BCG.[25]

Recurrent urinary tract infection

Recurrent UTI is a well established risk factor for the development of SCC, with a relative risk of 5.7 for a history of three or more UTIs. As with the other risk factors described above, recurrent UTI is associated with chronic inflammation of the urinary tract and the promotion of keratinising squamous metaplasia. This is supported by epidemiological data.[19,26] The enzyme cyclooxygenase-2 has been demonstrated to be markedly expressed in bladder SCC in particular; in one study, it was found in 100% of SCC and 100% of squamous metaplasia cases.[27] This is consistent with the aetiology of primary SCCs in their association with recurrent UTI. It is postulated that inflammation stimulates the production of cyclooxygenase-2 via bacterial lipopolysaccharides, which in turn activates nitrosamines (produced by patients with chronic UTI), enabling the progression to SCC.[27]

Neurogenic bladder

Neurogenic bladder associated with SCI following trauma or conditions such as spina bifida has been reported as a risk factor for developing bladder cancer.[1,28] A population-based study by West *et al* in 1999 identified bladder malignancy in 0.39% of a large SCI population, with primary SCC comprising 33% of bladder malignancies detected.[17] To some extent, this is believed to be related to the use of IDC. However, this is not thought to entirely explain the association.

Kalisvaart *et al* examined bladder cancer in SCI patients and found that over 50% did not have an IDC.[28] Rates of recurrent UTI in neurogenic bladder patients is significantly higher than in the rest of the population and an annual incidence of up to 25% has been reported.[29] Animal models have demonstrated that the SCI bladder predisposes to delayed clearance of infection and an exaggerated inflammatory response, with the severity of residual volumes having no predictive effect for rates of UTI.[29] It has therefore been suggested that the increased susceptibility of the neurogenic bladder to recurrent infection is mediated by an additional mechanism other than simply by changes in bladder physiology. This has been postulated to be a result of the differences in endogenous bacteria colonising the bladders of SCI patients.[29]

Results of case analysis

The results of this analysis of 90 cases of primary SCC supports the association between this malignancy and several of the well documented risk factors for its development, such as smoking and recurrent UTI. An interesting finding is the association observed between primary SCC and catheter use (identified in 13%), particularly CISC (with over 10% of patients in this series having performed CISC for a median duration of ten years).

To date, there have been several isolated case reports and small case series indicating a link between CISC and primary SCC.[2] However, the literature relating to this association is relatively scarce. The findings of our series suggest that it is not merely the presence of a neuropathic bladder or recurrent UTI alone that may contribute to the development of primary SCC but that the chronic use of CISC also has an important role.

The mechanism by which SCC develops in the CISC bladder has been proposed as a combination of keratinising squamous metaplasia (a premalignant condition), persistent (and often asymptomatic) bacteriuria and direct epithelial trauma.[2] This theory would therefore support the use of antimicrobial catheters to reduce bacteriuria in the hope of decreasing the synergistic effect of these factors. Notably, it would appear that the risk of SCC is elevated with the use of CISC in the presence of another risk factor for primary SCC (such as smoking), suggesting some underlying synergistic mechanism.

Progression from SCC in situ to muscle invasive disease can be rapid and so SCC in situ detected on biopsy should be closely monitored clinically.[30] In addition, as with our data, many tumours described histologically as primary SCCs are in fact urothelial malignancies with squamous differentiation. Making the correct distinction between these two diagnoses is important in the management and subsequent surveillance of the disease. The presence of squamous metaplasia or SCC in situ can often aid in making a histological diagnosis of primary SCC over other cancers with squamous differentiation.[30]

SCC generally carries a much poorer prognosis than urothelial cell cancer and advanced disease is usually identified at presentation. In our series, 40.0% of patients had pT3 or pT4 disease. While radical cystectomy remains the management of choice for primary SCC, the results from this analysis demonstrate that a substantial proportion of patients (43.3%) undergo local resection only (with or without chemotherapy or radiotherapy). Many patients did not undergo radical surgery owing to either advanced disease at presentation or not being fit enough for surgery because of other underlying co-morbidities. Whether to opt for partial cystectomy seems to be dependent on local practice as a choice for patients who are not medically fit to undergo radical cystectomy. However, there is some very limited evidence that in some cases with strict selection criteria, segmental resection may be a feasible choice for bladder SCCs if they are solitary and the rest of the urothelium remains clear of any premalignant lesions.[31]

As with all variants of bladder malignancy, early diagnosis is the key to improved outcomes, and at the present time, cystoscopy and biopsy or resection of the identified tumour remains the gold standard for detection and diagnosis of bladder malignancy. The data from our study indicate there is a relationship between CISC and development of primary SCC, and in light of the poor prognosis of the disease, it could be argued that increased surveillance for patients using CISC is justified to ensure early diagnosis. Nevertheless, the cost effectiveness of performing surveillance cystoscopy on patients undergoing ISC remains controversial.[14]

Although multiple surveillance regimens for patients with well established risk factors have been described in the literature, a clear consensus is still lacking. Navon *et al* recommend annual surveillance cystoscopy for all patients who have had SCI or recurrent UTI for ten years.[32]

Locke *et al* suggest performing annual urine cytology on high risk patients as an alternative non-invasive surveillance method.[11] However, while urine cytology may offer specificity in detection of malignancy, the ability of this test alone to exclude malignancy and negate the requirement for more invasive investigation remains inadequate,[33] particularly in catheterised patients.

The advent of cheaper, non-invasive investigations for detection of primary SCC offers a potential method for surveillance of high risk patients. Various biomarkers such as psoriasin, SCC antigen, Bcl-2, p53, nitric oxide, cyclooxygenase and cytokeratin have been investigated for their potential in detecting SCC.[2]

Research into identifying the optimum biomarker for detecting urothelial cell malignancies is currently ongoing.[34] This perhaps offers the greatest hope for devising a potential non-invasive, cost effective screening tool for SCC.

At present, there are no clear guidelines regarding the surveillance of patients specifically with IDCs or performing regular CISC bit it is generally accepted that all patients with 'red flag' symptoms such as haematuria should undergo full investigation for malignancy. As previous studies have suggested, haematuria is the most widely reported presenting symptom (45.6%).[1] It is important to remember that CISC may mask many of the presenting features of SCC. SCI patients also appear to present a particular challenge for detection and diagnosis of disease given high rates of abnormal presentation at a younger age[35] and late diagnosis. One study demonstrated that over 60% of SCI patients had an advanced stage of bladder malignancy at diagnosis (regardless of histological type).[36]

More understanding of the interplay between the different risk factors is also required. For example, recurrent UTI has been demonstrated to have a multiplicative interaction with smoking in increasing risk of bladder cancer,[19] and the combination of IDC and patients with a neuropathic bladder following SCI also poses a significantly increased risk compared with either in isolation.[20]

Study limitations

This study has obvious limitations in that it was a retrospective analysis. In addition, while every effort was made to remove ambiguous reports from the series, it was not possible to ensure conclusively that all cases were true primary bladder SCC rather than urothelial cell carcinoma with squamous differentiation. Another drawback is that although these data suggest that there may be a link between SCC and CISC, it is not possible to properly quantify the risk of developing SCC for the CISC population since the total number of patients who perform CISC is unknown, as is the percentage of these who go on to develop bladder SCC.

Conclusions

Further evidence of the role of CISC in primary SCC is required to justify invasive and expensive testing, and to determine exactly when surveillance of the bladder should begin for this group of patients. Owing to the poor prognosis of primary SCC compared with other bladder malignancies, it is imperative that a low threshold for investigation should be adopted in patients with risk factors for the disease as early detection is associated with improved outcomes. While it is good clinical practice to arrange urgent investigation of haematuria in patients performing CISC, the role of cystoscopic surveillance remains controversial. The development of urinary analysis of biomarkers offers a potential and useful means of surveillance for high risk patients in the future.

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