Arab Journal of Urology (2016) **14**, 183–191

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

ONCOLOGY/RECONSTRUCTION
REVIEW

Squamous cell carcinoma of the urinary bladder: Systematic review of clinical characteristics and therapeutic approaches

Jeremy W. Martin [a], **Estrella M. Carballido** [b], **Ahmed Ahmed** [a,c], **Bilal Farhan** [a], **Rahul Dutta** [a], **Cody Smith** [a], **Ramy F. Youssef** [a,*]

[a] *Department of Urology, University of California – Irvine, Orange, CA, USA*
[b] *Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Scottsdale, AZ, USA*
[c] *Department of Urology, Faculty of Medicine, Aswan University, Aswan, Egypt*

Received 13 April 2016, Received in revised form 24 June 2016, Accepted 3 July 2016
Available online 1 August 2016

KEYWORDS

Squamous cell carcinoma (SCC);
Bladder;
Bilharzial;
Radical cystectomy;
Radiotherapy

ABBREVIATIONS

B-SCC, bilharzial-associated SCC;
CISC, clean

Abstract ***Objective:*** To highlight the current understanding of the epidemiology, clinicopathological characteristics, and management of squamous cell carcinoma (SCC) of the bladder, as it accounts for 2–5% of bladder tumours, with a focus on non-bilharzial-associated SCC (NB-SCC). The standard treatment for bladder SCC remains radical cystectomy (RC). We present an updated clinical profile of bladder SCC and a review of NB-SCC therapeutic approaches, including RC, neoadjuvant and adjuvant treatments, radiotherapy, chemotherapy, and immunotherapy.

Methods: Using search terms relating to SCC, urinary bladder, and treatment modalities, we performed a search of the PubMed and Embase databases to identify NB-SCC treatment approaches and outcomes. Peer-reviewed English language reports from 1975 to present assessing SCC management were included. Two authors independently screened and extracted the data.

* Corresponding author at: Department of Urology, University of California, Irvine, 333 City Boulevard West, Suite 2100, Orange, CA 92868, USA. Fax: +1 (877) 829 7891.
E-mail address: ryaacoub@uci.edu (R.F. Youssef).

Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.aju.2016.07.001

intermittent self-catheterisation;
COX-2, cyclooxygenase 2;
DFS, disease-free survival;
FGF-2, fibroblast growth factor 2;
HER-2, human epidermal growth factor receptor 2;
HPV, human papilloma virus;
LVI, lymphovascular invasion;
LN, lymph node;
NAC, neoadjuvant chemotherapy;
NB-SCC, non-bilharzial SCC;
OS, overall survival;
PD-1, programmed cell death 1;
PD-L1, programmed death-ligand 1;
RC, radical cystectomy;
SCC, squamous cell carcinoma;
SCI, spinal cord injury;
SEER, Surveillance, Epidemiology, and End Results

Results: Of the 806 articles screened, 10 met the pre-defined inclusion criteria. RC was performed in seven of the 10 studies. Although radiotherapy alone yielded poor outcomes, preoperative radiotherapy and RC were associated with improved survival. There is little evidence supporting the use of chemotherapy in NB-SCC, and its efficacy in relation to RC is not known.

Conclusion: Based on current literature, there is insufficient evidence to provide a treatment recommendation for NB-SCC. Whilst RC is the standard of care, the role of preoperative radiotherapy should be revisited and compared to RC alone. Additional studies incorporating multimodal approaches, contemporary radiation techniques, and systemic therapies are warranted. Immunotherapy as a treatment for bladder SCC has yet to be investigated.

Introduction

Bladder cancer is the most common malignancy of the urinary tract, accounting for ~77,000 new cases and 16,000 deaths/year in the USA [1]. Although TCCs (urothelial carcinomas) represent the majority (~90–95%) of the bladder tumours in the USA, bladder cancer encompasses a wide spectrum of malignancies, including squamous cell carcinoma (SCC; 2–5%), adenocarcinoma (0.5–2%), small cell carcinoma (< 1%), and other less common histologies. Owing to its higher incidence, TCC has historically received the most research attention, whilst other histopathological types including SCC have been understudied.

SCC is divided into two subtypes, SCC associated with bilharzia infection (schistosomiasis), i.e. bilharzial-associated SCC (B-SCC) and SCC not associated with bilharziasis, i.e. non-bilharzial-associated SCC (NB-SCC). B-SCC and NB-SCC differ in their epidemiology, natural history, and clinicopathological features [2] (Table 1). B-SCC is predominantly found in regions where schistosomiasis is endemic, such as in the Middle East, Southeast Asia, and South America [3]. In the USA, NB-SCC has been reported in patients with spinal cord injury (SCI), particularly following long-term use of an indwelling catheter [4–6]. Patients with NB-SCC are generally diagnosed at a late stage and present with poor prognosis [3]. Both B-SCC and NB-SCC are treated with radical cystectomy (RC); the use of other treatments, including neoadjuvant and adjuvant therapies in conjunction with RC, is not well established. We summarise below the current understanding of the epidemiology and clinicopathological characteristics of SCC and systematically review management strategies for SCC, with a focus on NB-SCC.

Methods

A search of the PubMed and Embase databases was performed using search terms 'squamous cell carcinoma' AND 'urinary bladder' AND 'treatment' AND ('cystectomy' OR 'radiotherapy' OR 'chemotherapy' OR 'immunotherapy'). The search, which was conducted in February 2016, included all English language publica-

Table 1 Epidemiological and clinicopathological characteristics of B-SCC and NB-SCC SCC of the urinary bladder.

	B-SCC	NB-SCC
Geography	Middle East, Southeast Asia, South America	Western countries
% of bladder tumours	20–30 (>50 in the past)	2–5
Age	Fifth decade	Seventh decade
Male:Female	5:1	3:2
Major predisposing factors	Bilharzial cystitis, UTIs	Indwelling catheters, chronic inflammation, bladder irritants, UTIs
Principal symptoms	Haematuria, irritative bladder symptoms	Haematuria
Stage	Mostly advanced	Mostly advanced
Grade	50% low grade	Mostly high grade
LN metastasis, %	18	8–10
Standard treatment	RC	RC
Prognosis (5-year survival), %	~50–60	33– 48
Recurrence	Mostly local	Mostly local
Prevention	Snail control and anti-bilharzial drugs	Avoidance of bladder irritants, including prolonged indwelling catheterisation

tions from January 1975 to January 2016. A total of 806 entries were generated from the initial screen after combining the results from both databases and removing duplicates. Pre-defined exclusion criteria included review articles, case reports, abstracts without corresponding publications, studies with limited sample sizes (defined as <25 for retrospective analyses), studies considering histologies other than pure SCC, and studies otherwise not related to the treatment and management of NB-SCC. Articles were assessed for validity and selected for inclusion and exclusion by the first and senior authors, who reached consensus after discussion with the other authors.

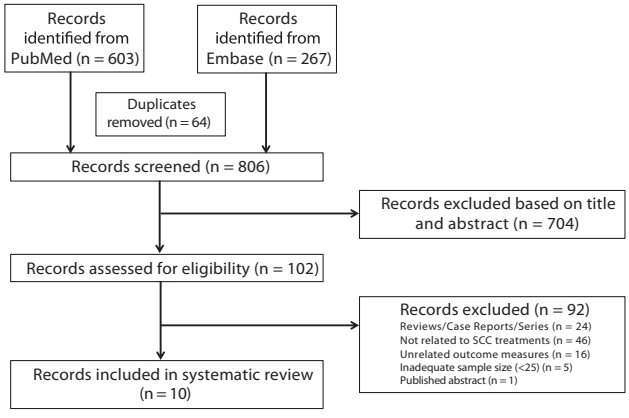

Figure 1 Flowchart of studies selected for the systematic review.

Table 2 Treatments, survival rates, and levels of evidence of reviewed publications.

Reference	Year	Level of evidence	*N*	Treatment modality	5-year OS rates, %
Richie et al. [32]	1976	III	33	RC	48
Kassouf et al. [28]	2007	III	27	RC + neoadjuvant chemotherapy or preoperative radiation	47.6 at 2 years
Jones et al. [37]	1980	III	51	Radiation + elective RC	16
Rundle et al. [35]	1982	III	114	Radiation	1.9
Quilty et al. [36]	1986	III	107	Radiation	18.3 at 3 years
Johnson et al. [34]	1976	III	90	RC + preoperative radiation	34 (17.7 radiation alone)
Prempree et al. [39]	1984	III	52	RC + preoperative radiation	40 (16 radiation alone)
Swanson et al. [40]	1990	III	25	RC + preoperative radiation	50
Rausch et al. [47]	2012	III	31	RC ± neoadjuvant chemotherapy, chemo-irradiation	26
Galsky et al. [45]	2007	II	8	Chemotherapy	Median survival 8.9 months

Results

Of the 806 studies queried, 10 met the pre-defined eligibility criteria (Fig. 1). Seven studies involved RC as the treatment for NB-SCC, with some incorporating the use of radiation in addition to RC, whilst the remaining studies used radiotherapy alone and chemotherapy alone as treatments (Table 2) [28,32,34–37,40,45,47]. Preoperative radiotherapy with RC was associated with improved outcomes, although the comparison group in these studies was irradiation alone. There was no evidence that chemotherapy improves survival over RC. No studies assessing immunotherapy as a treatment for bladder SCC were retrieved.

Evidence was primarily Level III; no Level I studies were obtained. Level IV and poorer evidence was excluded. Given the rarity of SCC and lack of high-quality studies, the discussion below incorporates related studies such as those of B-SCC and TCC in order to most accurately characterise the rationale of specific treatments and the current understanding of SCC management.

Recent findings

Epidemiology and aetiology

In countries such as Egypt where schistosomiasis was endemic, SCC has historically represented the predominant histological type of bladder cancer, constituting ~60% of bladder tumours in a large case series during the 1990s [7]. Schistosomiasis is considered the major predisposing factor for B-SCC and is responsible for the high incidence of SCC in these regions [8]. B-SCC displays an average age of diagnosis in the fifth decade and a male to female ratio of about 5:1, probably relating to the increased exposure of male farmers to schistosome infestation in the fields [3]. With the increasing use of preventative measures involving snail control and anti-bilharzial drugs, the histopathological profile of bladder cancer has evolved significantly in the past three decades. Whilst the frequency of SCC in Egypt in the 1970–1980s was 60–70%, retrospective analyses indicate that SCC is now less common, representing 20–30% of contemporary Egyptian bladder cancers [9].

In Western countries, where NB-SCC is the predominant subtype, patients are typically diagnosed in the seventh decade and have poor survival outcomes [2]. NB-SCC has a slight male and African-American preponderance in the USA, with a male to female ratio of about 3:2 and an African-Americans to Whites ratio of 2:1 [10]. NB-SCC has been associated with neurogenic bladder dysfunction and chronic bladder irritation from various causes, including prolonged indwelling catheterisation, BOO, and urinary stasis [3,11]. Older studies indicated a 16- to 28-fold increased risk of SCC in paraplegic patients [6] and a NB-SCC incidence of 10% in patients with an indwelling catheter at $\geqslant$10 years [12]. These studies formed the basis for clean, intermittent self-catheterisation (CISC) in patients with SCI. Initial reports suggested that CISC reduced the risk of cancer development, but SCC following CISC has nevertheless been described in several recent case reports [13]. A large study of 43,561 patients with SCI from Central Europe identified no significant difference in risk of bladder cancer between patients with SCI and the general population, suggesting the link to bladder cancer was primarily related to indwelling catheters, UTIs, and exposure to carcinogens [14].

In both SCC and TCC, tobacco smoking has been reported as a major risk factor for bladder cancer. Bladder irritants, UTIs, and chronic inflammation are thought to create an environment abundant in growth factors and cytokines favouring cell proliferation, migration, angiogenesis, and inhibition of apoptosis, resulting in squamous metaplasia, dysplasia, and cancer [15]. The stresses to the bladder mucosa resulting from UTIs, catheterisation, and other bladder irritants may therefore drive inflammation and carcinogenic changes that facilitate squamous metaplasia and SCC progression.

Squamous metaplasia involves non-keratinising or keratinising whitish plaques floating on an inflamed urothelium and has been linked to SCC [16]. The risk of bladder cancer development following squamous metaplasia is 21–42% [17], although the precise oncogenic pathway is unclear. Clinical features of squamous metaplasia include haematuria, urgency, frequency, and obstruction, similar to symptoms of SCC [16]. Keratinising squamous metaplasia has been observed in a majority (28 out of 45) of cases of NB-SCC [18], but has also been suggested as a normal histological variation in female patients. At this time, there is insufficient evidence to suggest that squamous metaplasia is a premalignant finding and aggressive surgical treatment is not recommended.

In B-SCC, several aetiological studies have suggested that the bacterial and viral infections associated with bilharziasis, rather than the parasite itself, are responsible for bladder carcinogenesis [3]. Urinary bacteria, including *Escherichia coli*, *Proteus*, and *Streptococcus faecalis*, have been implicated in the development of squamous metaplasia. The carcinogenic mechanism probably involves nitrosamine production and release of free carcinogenic products through secretion of β-glucoronidase [19]. In patients with SCI, bacterial infections relating to UTIs are frequently implicated in the development of NB-SCC. Vitamin A deficiency has also been associated with the development of both B-SCC and NB-SCC, as has systemic therapy with cyclophosphamide, a known risk factor for TCC [20].

Human papilloma virus (HPV) has been linked to genitourinary cancers and SCC, although its relationship with SCC of the bladder is controversial. Interestingly, HPV has been identified as carcinogenic in various SCCs, including the anogenital and oropharyngeal regions, suggesting a potential infectious role in bladder SCC development. Given these associations between HPV and cancer and the fact that viral infections are associated with B-SCC progression, multiple research groups have investigated whether a link exists between HPV infection and SCC. The literature concerning the putative role of HPV in SCC pathogenesis provides conflicting evidence. Whilst some studies have identified an association between HPV and SCC [21], other studies have reported no association between high-risk HPV and bladder SCC pathogenesis [22]. A causal relationship between HPV and SCC appears unlikely at this time, but warrants further investigation.

Clinical and pathological features of SCC

Haematuria is the principal symptom and is observed in most cases. However, some patients will present with irritative bladder symptoms such as frequency, urgency,

or pain. Symptoms of pelvic pain, back pain, and/or hydronephrosis are suggestive of advanced disease. In addition, patients often present with chronic cystitis and recurrent UTIs; it has been reported that up to 93% of patients concurrently present with UTI at the time of diagnosis [3]. These symptoms are often present for protracted intervals before the definitive diagnosis. Overall, the prognosis of NB-SCC is poor, with most patients dying within 3 years and a 5-year survival rate of 33–48% [23].

SCC is described as an epithelial neoplasm exclusively displaying histological features such as squamous pearls, intercellular bridges, and keratohyalin granules [23]. Although squamous features are present in TCC variants with mixed histology, the definition of SCC or pure SCC is reserved for tumours that only contain squamous components without any evidence of urothelial components [24]. On cystoscopy, SCC tumours are typically large solitary masses, extensive, and associated with leucoplakia. NB-SCC has a preference for the trigone region, but may also occupy any region of the bladder, including diverticula, or extend locally to the urethra or ureters [2,3]. NB-SCC tumours are rarely superficial, and early stage tumours, i.e. Ta and T1 tumours, are uncommonly encountered. In a case series of patients with NB-SCC, T3 lesions (invasion into the perivesical fat) represented the most common stage and comprised 60% of the cases, whereas ~2% were T1 [18]. A population-based analysis of 614 patients with NB-SCC using the Surveillance, Epidemiology, and End Results (SEER) programme showed that the most frequent stage was T3 (42.3%), and the most common histological grades were II (37.3%) and III (42.5%) [25]. These findings support that NB-SCC tumours are locally advanced with a moderate-to-high histological grade, in contrast to tumours of B-SCC, which are similarly advanced but are usually well differentiated [15]. NB-SCC tumours also tend to display low rates of lymphovascular invasion (LVI) and lymph node (LN) metastasis. A recent study of patients with SCC revealed a low incidence of LVI (13%) and LN metastasis (18%) in 360 RC cases [26].

Prognostic factors and survival outcomes

SCC prognostic factors and cancer-specific mortality with respect to other bladder cancers have gradually been elucidated. Pathological prognostics of SCC include tumour stage, grade, LVI, and presence of LN involvement [7,8,26]. A recent analysis of all stage III and stage IV bladder cancer cases in Ontario, Canada, noted that whilst the disease course of SCC was more rapid compared to TCC, the 5-year overall survival (OS) of SCC was equivalent to TCC after adjusting for covariates [24]. These findings were in contrast to a previous analysis using the SEER database, which showed that SCC had a higher overall and cancer-specific mortality than TCC [27]. It is unclear how to reconcile the differences between these studies; the discrepancies may represent differences in disease trajectory, where patients with SCC have poorer survival rate at 2 years, but equivalent mortality when compared to patients with TCC at 5 years.

About 90% of mortality in SCC is due to local pelvic recurrence, commonly at the anastomosis between the bladder and the urethra or the ureters. Distant metastases are uncommon, with an incidence of 8–10% in NB-SCC [2]. Death occurs from locoregional progression as a result of ureteric or bladder neck obstruction and kidney failure [28]. These complications highlight the importance of local control and of exploring other therapeutic options to reduce the incidence of pelvic recurrence [16].

Molecular biomarkers have also been explored for their prognostic ability in predicting oncological outcomes. Youssef et al. [15] reported that fibroblast growth factor 2 (FGF-2) overexpression was associated with aggressive pathological features of SCC including LVI and LN involvement, and poorer overall outcomes following RC. The authors suggested both a prognostic and therapeutic role in targeting FGF-2. Youssef et al. [15] additionally observed that cyclooxygenase 2 (COX-2) alterations were associated with high stage and grade and predicted poor outcomes in both NB-SCC and B-SCC. This study highlights a possible preventive or adjunct role of COX-2 inhibitors in the prevention or treatment of SCC. In a study comparing fourteen prognostic biomarkers for SCC, a panel of five markers, including COX-2, FGF-2, p53, Bax, and epidermal growth factor receptor (EGFR), was determined to best represent outcomes after RC [29]. Human epidermal growth factor receptor 2 (HER-2) oncoprotein expression was also recently identified to be higher in SCC tumours, suggesting that HER-2-positive tumours could benefit from targeted agents [30]. As variations in specific biomarker expression may be associated with differences in outcomes and/or patient responsiveness to therapies, these biomarkers may be utilised to guide the optimal treatment approach.

Prevention and detection

Given that bladder SCC presents at a late stage and portends poor prognosis, it is important that future research endeavours support the early detection of squamous cell tumours. Patients, especially those with SCI, should avoid chronic infections and other bladder irritants (e.g. long-term catheterisation and smoking). It is recommended that patients with SCI, especially those with indwelling catheters, chronic and recurrent UTIs, undergo annual screening cystoscopy and urine cytology. Reducing the chronic infections and risk factors

associated with SCC (such as using CISC, rather than indwelling catheters), may decrease the incidence of SCC. Prevention of B-SCC involves elimination of the schistosome intermediate snail host and the use of anti-bilharzial therapies and screening in endemic areas. These measures have significantly reduced the incidence of SCC in Egypt.

Advances in the molecular biology may facilitate the early detection of NB-SCC. Psoriasin, a calcium-binding protein expressed by squamous epithelia, has been described as a potential marker for SCC [3]. Galectin 3 has also been reported as a diagnostic marker for both TCC and SCC, but the prognostic significance is unknown. Other biomarkers, including Forkhead box protein P3 (Foxp3), may allow the early diagnosis of squamous differentiation and SCC [31].

Discussion

There is a paucity of high quality prospective studies pertaining to SCC treatment options, particularly for NB-SCC. As SCC is an uncommon disease, conducting large-scale, well-controlled prospective studies would be very challenging. Many of the treatment recommendations for SCC are based on small observational studies. At this time, RC is the 'gold standard' treatment for SCC, but other management strategies incorporating the use of radiotherapy and chemotherapy in the neoadjuvant or adjuvant setting have been employed with varying successes. Preoperative radiation followed by RC appears to confer a survival advantage over RC alone, although the current evidence is insufficient to conclude definitively. Further studies are needed to support treatment recommendations. We describe below major SCC treatment paradigms, supported by relevant studies.

RC

RC and urinary diversion is the standard treatment of SCC of the urinary bladder [2]. There is a general consensus regarding the necessity for radical surgical treatment, as it allows disease control and better survival than partial cystectomy, radiotherapy, and chemotherapy. Richie et al. [32] reported a 5-year survival of 48% in patients with NB-SCC undergoing RC, but a subsequent analysis of the data determined the survival rate to be lower. More recently, a retrospective analysis by Kassouf et al. [28] reported that treatment with RC was associated with recurrence-free survival and noted that all cases surviving >2 years had undergone RC. SCC frequently presents as a bulky locally advanced disease, most of the time unsuitable for partial cystectomy and sometimes unresectable by RC. There have not been any large series considering partial cystectomy in the setting of SCC. To date, we believe RC with lymphadenectomy is still the 'gold standard' treatment [18,33]. Whilst RC is the standard of care, there is still a high incidence of recurrence and low OS. It is believed that neoadjuvant or adjuvant treatments (radiotherapy ± systemic therapy) could minimise recurrence and improve survival. These multimodal approaches involving the combination of RC with neoadjuvant treatments have been reported and are discussed below.

Radiation therapy

Radiation as a primary therapy has previously been associated with poor outcomes [34–37]. However, it appears to provide some benefit as a preoperative therapy prior to RC. Prospective randomised studies in B-SCC have suggested that treatment with preoperative radiotherapy improves disease-free survival (DFS) over RC alone [38]. Several studies of NB-SCC have also reported higher 5-year survival in patients treated with preoperative radiation and RC vs those treated with radiation alone or other treatments [34,39,40]. Combined therapy involving preoperative radiation with RC both enhanced 5-year DFS (40%) over radiation alone (16%) and lowered rates of recurrence, suggesting the role of preoperative radiotherapy in minimising locoregional failures [39,40]. As integrating preoperative radiation with RC is associated with survival advantages, preoperative radiation and RC with urinary diversion may represent an approach that warrants further exploration in a prospective randomised study. However, preoperative radiation may carry the potential risk of adding technical difficulties and possible intraoperative complications due to inflammation and adhesions between tissue planes in the radiated area. To date, this combined approach is not considered standard of care for these patients.

Adjuvant radiotherapy has historically been associated with serious side-effects including intestinal obstruction and urinary fistulae. In B-SCC, a recent study of patients determined that those not receiving adjuvant radiotherapy had a DFS of 29% compared to 48% for those who received adjuvant radiotherapy [41]. Given advances in radiation techniques and other promising contemporary studies of B-SCC [42], postoperative radiotherapy for SCC should also be revisited.

Radiotherapy with concomitant chemotherapy may also function as a useful alternative for unresectable bladder tumours or in cases where bladder preservation is desired [43]. Thus, whilst there may be a potential clinical advantage in combining radiation with RC, there is no consensus given the limited data and lack of large randomised studies with radiotherapy in SCC. Given that many of the published studies involving radiation therapy and bladder SCC are older trials, and the recent advancements in high precision radiotherapy techniques, the potential use of radiation therapy for SCC

should be explored further, particularly in conjunction with RC and other systemic therapies.

Chemotherapy

In contrast to the chemosensitive TCC, SCC of the bladder has been considered a chemotherapy-resistant disease, as it has low responsiveness to standard chemotherapy regimens. Whilst treatment with M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) was ineffective in patients with non-TCC [44], Galsky et al. [45] published the first prospective study of patients with unresectable non-TCC, which included eight patients with pure SCC. The regimen of ifosfamide, paclitaxel, and cisplatin was active in patients with SCC, reporting a median survival of 8.9 months and complete remission in two of the eight SCC cases. This is the only prospective study in the USA that specifically included patients with non-urothelial bladder cancer showing clinical benefit in this population. In addition, a study of B-SCC found that neoadjuvant chemotherapy (NAC) with gemcitabine and cisplatin induced high response rates with a moderate toxicity profile [46]. Additional studies with larger samples are needed to establish whether chemotherapy regimens are effective in treatment of SCC. The performance of chemotherapy relative to RC with and without radiation should also be assessed.

The use of NAC or adjuvant chemotherapy in conjunction with RC has been explored, but its effectiveness is uncertain [47]. Gad el Mawla et al. [48] previously showed promising outcomes in treating B-SCC with neoadjuvant epirubicin followed by RC and adjuvant epirubicin. However, there were no confirmatory studies and this approach did not gain widespread clinical utilisation. The largest retrospective study in the USA was reported by the MD Anderson Cancer Center group [28]. In all, 27 patients with resectable tumours (T2–T4b) were included, of which eight received preoperative chemotherapy and/or radiation therapy. Due to rapid progression of disease, only three of the eight treated with neoadjuvant therapy (one with NAC, one with radiation, and one with chemo-irradiation) underwent RC. The 2-year OS of the overall study group was 47.6%. No conclusion was made on the therapeutic value of neoadjuvant therapies. Data on adjuvant chemotherapy are also lacking large, well-designed studies; studies of adjuvant treatments have generally involved the continued use of chemotherapy regimens in select patients who previously responded to NAC.

Immunotherapy

Immunotherapy represents a promising adjunct to conventional RC for SCC treatment. Intravesical BCG is the standard of care following resection of non-muscle-invasive TCC. The exact mechanism is still unknown, but BCG-induced Th1 and cytotoxic cellular immune responses have been implicated [49]. Recent studies in TCC have also explored potential immunotherapeutic uses in targeting the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis. PD-1/PD-L1 pathway blockade by antibody appears to reduce T-cell proliferation and Th1 responses [49]. PD-L1 is expressed on activated T-cells and is upregulated in TCC. Immune checkpoint inhibitors have demonstrated activity in metastatic urothelial carcinoma [50]. A new PD-L1 agent atezolizumab showed durable activity and an objective response rate of 26% in platinum-refractory metastatic TCC [51]. Immunotherapy has proven to offer clinical responses in patients with platinum-refractory metastatic TCC and may represent as well a new treatment option for non-urothelial carcinomas including SCC. Whilst there are currently no data supporting the use of immunotherapy in SCC of the bladder, it appears to represent an attractive future approach, as the clinical benefits appear independent of primary tumour site or histology.

Conclusion

The worldwide incidence of SCC is decreasing. Chronic inflammation is the main predisposing factor in NB-SCC. Due to rarity of the disease, there is a lack of Level I evidence guiding management of SCC. RC remains the standard treatment for SCC, although local recurrences are common. Given recent advances in radiotherapy and previous studies suggesting improved outcomes with radiotherapy, the role of neoadjuvant/adjuvant radiation should be re-evaluated. Immunotherapy with new agents targeting PD-1 and PD-L1 may also improve clinical outcomes. Given the rarity of non-urothelial histologies, SCC should be included in clinical trials using immunotherapy, as tumour response is independent of location of primary tumour and histology. Use of biomarkers in conjunction with classic pathological prognosticators such as stage, grade, LN involvement and LVI may also improve prognosis and guide multimodal treatment approaches in the era of personalised medicine.

Conflicts of interest

None declared.

Source of funding

None.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;**66**:7–30.

[2] Abol-Enein H, Kava BR, Carmack AJ. Nonurothelial cancer of the bladder. *Urology* 2007;**69**:93–104.

[3] Shokeir AA. Squamous cell carcinoma of the bladder: pathology, diagnosis and treatment. *BJU Int* 2004;**93**:216–20.

[4] Kalisvaart JF, Katsumi HK, Ronningen LD, Hovey RM. Bladder cancer in spinal cord injury patients. *Spinal Cord* 2010;**48**:257–61.

[5] Welk B, McIntyre A, Teasell R, Potter P, Loh E. Bladder cancer in individuals with spinal cord injuries. *Spinal Cord* 2013;**51**:516–21.

[6] Kaufman JM, Fam B, Jacobs SC, Gabilondo F, Yalla S, Kane JP, et al. Bladder cancer and squamous metaplasia in spinal cord injury patients. *J Urol* 1977;**118**:967–71.

[7] Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1026 cases. *J Urol* 1997;**158**:393–9.

[8] Ghoneim MA, Abdel-Latif M, el-Mekresh M, Abol-Enein H, Mosbah A, Ashamallah A, et al. Radical cystectomy for carcinoma of the bladder: 2720 consecutive cases 5 years later. *J Urol* 2008;**180**:121–7.

[9] Felix AS, Soliman AS, Khaled H, Zaghloul MS, Banerjee M, El-Baradie M, et al. The changing patterns of bladder cancer in Egypt over the past 26 years. *Cancer Causes Control* 2008;**19**:421–9.

[10] Porter MP, Voigt LF, Penson DF, Weiss NS. Racial variation in the incidence of squamous cell carcinoma of the bladder in the United States. *J Urol* 2002;**168**:1960–3.

[11] Navon JD, Soliman H, Khonsari F, Ahlering T. Screening cystoscopy and survival of spinal cord injured patients with squamous cell cancer of the bladder. *J Urol* 1997;**157**:2109–11.

[12] Locke J, Hill D, Walzer Y. Incidence of squamous cell carcinoma in patients with long-term catheter drainage. *J Urol* 1985;**133**:1034–5.

[13] Casey RG, Cullen IM, Crotty T, Quinlan DM. Intermittent self-catheterization and the risk of squamous cell cancer of the bladder: an emerging clinical entity? *Can Urol Assoc J* 2009;**3**:E51–4.

[14] Pannek J. Transitional cell carcinoma in patients with spinal cord injury: a high risk malignancy? *Urology* 2002;**59**:240–4.

[15] Youssef R, Kapur P, Kabbani W, Shariat SF, Mosbah A, Abol-Enein H, et al. Bilharzial vs non-bilharzial related bladder cancer: pathological characteristics and value of cyclooxygenase-2 expression. *BJU Int* 2011;**108**:31–7.

[16] Rausch S, Lotan Y, Youssef RF. Squamous cell carcinogenesis and squamous cell carcinoma of the urinary bladder: a contemporary review with focus on nonbilharzial squamous cell carcinoma. *Urol Oncol* 2014;**32**, 32.e11-6.

[17] Khan MS, Thornhill JA, Gaffney E, Loftus B, Butler MR. Keratinising squamous metaplasia of the bladder: natural history and rationalization of management based on review of 54 years experience. *Eur Urol* 2002;**42**:469–74.

[18] Lagwinski N, Thomas A, Stephenson AJ, Campbell S, Hoschar E, El-Gabry E, et al. Squamous cell carcinoma of the bladder: a clinicopathologic analysis of 45 cases. *Am J Surg Pathol* 2007;**31**:1777–87.

[19] Hicks RM, Ismail MM, Walters CL, Beecham PT, Rabie MF, El Alamy MA. Association of bacteriuria and urinary nitrosamine formation with Schistosoma haematobium infection in the Qalyub area of Egypt. *Trans R Soc Trop Med Hyg* 1982;**76**:519–27.

[20] Stein JP, Skinner EC, Boyd SD, Skinner DG. Squamous cell carcinoma of the bladder associated with cyclophosphamide therapy for Wegener's granulomatosis: a report of 2 cases. *J Urol* 1993;**149**:588–9.

[21] Shaker OG, Hammam OA, Wishahi MM. Is there a correlation between HPV and urinary bladder carcinoma? *Biomed Pharmacother* 2013;**67**:183–91.

[22] Westenend P, Stoop J, Hendriks J. Human papillomaviruses 6/11, 16/18 and 31/33/51 are not associated with squamous cell carcinoma of the urinary bladder. *BJU Int* 2001;**88**:198–201.

[23] Manunta A, Vincendeau S, Kiriakou G, Lobel B, Guille F. Non-transitional cell bladder carcinomas. *BJU Int* 2005;**95**:497–502.

[24] Izard JP, Siemens DR, Mackillop WJ, Wei X, Leveridge MJ, Berman DM, et al. Outcomes of squamous histology in bladder cancer: a population-based study. *Urol Oncol* 2015;**33**, 425.e7-13.

[25] Abdollah F, Sun M, Jeldres C, Schmitges J, Thuret R, Djahangirian O, et al. Survival after radical cystectomy of non-bilharzial squamous cell carcinoma vs urothelial carcinoma: a competing-risks analysis. *BJU Int* 2012;**109**:564–9.

[26] Spradling K, Abol-Enein H, Mosbah A, Okhunov Z, Landman J, Shokeir A, et al. PD41-07 prognostic significance of lymphovascular invasion in patients with squamous cell carcinoma in comparison to urothelial carcinoma of the bladder. *J Urol* 2015;**193**:e842–3.

[27] Scosyrev E, Noyes K, Feng C, Messing E. Sex and racial differences in bladder cancer presentation and mortality in the US. *Cancer* 2009;**115**:68–74.

[28] Kassouf W, Spiess PE, Siefker-Radtke A, Swanson D, Grossman AM, Kamat AM, et al. Outcome and patterns of recurrence of nonbilharzial pure squamous cell carcinoma of the bladder: a contemporary review of The University of Texas M D Anderson Cancer Center experience. *Cancer* 2007;**110**:764–9.

[29] Youssef RF, von Rundstedt FC, Kapur P, Mosbah A, Abol-Enein H, Ghoneim M, et al. Utility of biomarkers in the prediction of oncologic outcome after radical cystectomy for squamous cell carcinoma. *J Urol* 2015;**193**:451–6.

[30] Hammam O, Nour HH, Mosaad M, Akl M, Khalil H, Al Ganzory H, et al. The clinical significance of HER2 protein amplification/expression in urinary bladder lesion. *Arab J Urol* 2015;**13**:146–52.

[31] Phe V, Roupret M, Cussenot O, Chartier-Kastler E, Game X, Comperat E. Forkhead box protein P3 (Foxp3) expression serves as an early chronic inflammation marker of squamous cell differentiation and aggressive pathology of urothelial carcinomas in neurological patients. *BJU Int*. 2015;**115**(Suppl. 6):28–32.

[32] Richie J, Waisman J, Skinner D, Dretler S. Squamous carcinoma of the bladder: treatment by radical cystectomy. *J Urol* 1976;**115**:670–2.

[33] Serretta V, Pomara G, Piazza F, Gange E. Pure squamous cell carcinoma of the bladder in western countries. Report on 19 consecutive cases. *Eur Urol* 2000;**37**:85–9.

[34] Johnson DE, Schoenwald MB, Ayala AG, Miller LS. Squamous cell carcinoma of the bladder. *J Urol* 1976;**115**:542–4.

[35] Rundle JS, Hart AJ, McGeorge A, Smith JS, Malcolm AJ, Smith PM. Squamous cell carcinoma of bladder. A review of 114 patients. *Br J Urol* 1982;**54**:522–6.

[36] Quilty PM, Duncan W. Radiotherapy for squamous carcinoma of the urinary bladder. *Int J Radiat Oncol Biol Phys* 1986;**12**:861–5.

[37] Jones MA, Bloom HJ, Williams G, Trott PA, Wallace DM. The management of squamous cell carcinoma of the bladder. *Br J Urol* 1980;**52**:511–4.

[38] Ghoneim MA, Ashamallah AK, Awaad HK, Whitmore Jr WF. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. *J Urol* 1985;**134**:266–8.

[39] Prempree T, Amornmarn R. Radiation management of squamous cell carcinoma of the bladder. *Acta Radiol Oncol* 1984;**23**:37–42.

[40] Swanson DA, Liles A, Zagars GK. Preoperative irradiation and radical cystectomy for stages T2 and T3 squamous cell carcinoma of the bladder. *J Urol* 1990;**143**:37–40.

[41] Abdel Raheem AM, Hameed DA, ElGanainy EO, Mosad E, Abdelwanis ME, Kamel NA, et al. Can Bcl-XL expression predict the radio sensitivity of bilharzial-related squamous bladder carcinoma? A prospective comparative study. *BMC Cancer* 2011;**11**:16.

[42] El-Monim HA, El-Baradie MM, Younis A, Ragab Y, Labib A, El-Attar I. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. *Urol Oncol* 2013;**31**:359–65.

[43] Higano CS, Tangen CM, Sakr WA, Faulkner J, Rivkin SE, Meyers FJ, et al. Treatment options for muscle-invasive urothelial cancer for patients who were not eligible for cystectomy or neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin: report of Southwest Oncology Group Trial 8733. *Cancer* 2008;**112**:2181–7.

[44] Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988;**139**:461–9.

[45] Galsky MD, Iasonos A, Mironov S, Scattergood J, Donat SM, Bochner BH, et al. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. *Urology* 2007;**69**:255–9.

[46] Khaled HM, Hamza MR, Mansour O, Gaafar R, Zaghloul MS. A phase II study of gemcitabine plus cisplatin chemotherapy in advanced bilharzial bladder carcinoma. *Eur J Cancer* 2000;**36** (Suppl. 2):34–7.

[47] Rausch S, Hofmann R, Knobloch R. Nonbilharzial squamous cell carcinoma and transitional cell carcinoma with squamous differentiation of the lower and upper urinary tract. *Urol Ann* 2012;**4**:14–8.

[48] Gad el Mawla N, Mansour MA, Eissa S, Ali NM, Elattar I, Hamza MR, et al. A randomized pilot study of high-dose epirubicin as neoadjuvant chemotherapy in the treatment of cancer of the bilharzial bladder. *Ann Oncol* 1991;**2**:137–40.

[49] Wu Y, Enting D, Rudman S, Chowdhury S. Immunotherapy for urothelial cancer: from BCG to checkpoint inhibitors and beyond. *Expert Rev Anticancer Ther* 2015;**15**:509–23.

[50] Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* 2014;**515**:558–62.

[51] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden AV, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;**387**:1909–20.