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SQUAMOUS CELL CARCINOMA OF URINARY BLADDER- A REVIEW

General Surgery

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ABSTRACT

Bladder cancer is the fourth most commonly diagnosed malignancy in men and the eighth most common in women. It represents a spectrum of disease, ranging from superficial, well differentiated disease, which does not significantly impact survival, to highly malignant tumors for which long term survival may be dismal. The vast majority of primary bladder tumors found in the United States are of transitional cell origin (90%-95%).Squamous-cell carcinoma (3%-5%) and adenocarcinoma(1%) are found in certain subsets of patients. This is in distinct contrast to primary bladder malignancies in countries such as Egypt, where the majority of bladder cancers are of squamous-cell-type. Chronic inflammation of the bladder, due to infestation by Schistosomahaematobium, is largely responsible for this finding. Malignancies such as sarcoma,pheochromocytoma, carcinoid, and small cel-ltumor are found infrequently. Leiomyosarcoma is the most common bladder sarcoma of the adult population, whereas rhabdomyosarcoma is the most frequently seen sarcoma in children. We will review the evaluation and current therapy for Squamous cell carcinoma of Urinary Bladder.

Aim And Objective:

The spectrum of bladder tumours is broad and includes TCC, adenocarcinoma, leiomyomas and squamous cell carcinoma (SCC). TCC is the most prevalent tumour and therefore has been the most extensively studied. SCC constitutes only a small percentage of all bladder tumours in nonbilharzial areas and therefore it has received less attention. The aim of this review is to assess publications on SCC in nonbilharzial regions. The epidemiology, pathogenesis and clinicopathological features of the two subpopulations of SCC (nonbilharzial and bilharzial) differ . Our aim is to highlight the current understanding of the epidemiology, clinico pathological characteristics, and management of squamous cell carcinoma(SCC) of the bladder, , 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.

KEYWORDS

INTRODUCTION

Squamous cell carcinoma (SCC) can occur in both nonbilharzial and bilharzial bladders; the two subtypes differ in epidemiology, pathogenesis and clinicopathological features. The nonbilharzial type occurs in Western countries and represents <5% of all vesical tumours; it occurs most often in the seventh decade with a slight male predominance.

Squamous cell carcinoma of the bladder within the United States is most commonly associated with chronic bladder irritation. Indwelling bladder catheters and bladder calculi, which are commonly seen in patients with spinal cord injury or neuromuscular disease, are major risk factors for development of this form of bladder cancer.Fortunately, the management of bladder dysfunction in this patient population has undergone significant advancements within the last 20 years, and it is believed that these modifications will decrease the incidence of squamous cell carcinoma. Squamous cell carcinoma is found in bladder diverticuli, and one must exclude this form of primary bladder cancer in any patient who presents with hematuria and a bladder diverticuli.

The main symptom is haematuria.

Patients are usually diagnosed at an advanced stage and most of the tumours are of moderate and high grades.At cystoscopy tumours are predominantly ulcerative and commonly involve the trigone and lateral walls. Although distant metastasis is infrequent (8–10%) the prognosis is grave and most patients die after failure of locoregional control; radical cystectomy provides the best therapy. To avoid nonbilharzial SCC, patients with spinal cord injury should be free of catheterization if possible. The outcome can be improved by early detection with frequent cytology, cystoscopy and biopsy. Bilharzial SCC occurs commonly in the Middle East, South-east Asia and South America where schistosomiasisis endemic. In an Egyptian series SCC represented 59% of 1026 cystectomy specimens. The tumour is diagnosed in the fifth decade, and five times more common in men than women. Bladder carcinogenesis is probably related to bacterial and viral infections, commonly associated with bilharzial infestation rather than the parasite itself. The presentation is often with irritative

bladder symptoms and haematuria, and many patients present at an advanced stage, although most tumours are of low and moderate grades. At cystoscopy tumours are predominantly nodular and usually arise from the upper vesical hemisphere. Lymph-node metastasis occurs in 19% and significantly decreases survival; radical cystectomy remains the main treatment, giving a 5-year survival rate of 50%. Early detection improves the therapeutic yield and prevention is possible by combining snail control and mass therapy of the infested rural population by oral antibilharzial drugs.

The standard treatment for bladder SCC remains radical cystectomy (RC). The article presents 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.

SCC IN THE NONBILHARZIAL BLADDER
EPIDEMIOLOGY

In Western regions pure SCC of the bladder constitutes 1.2–4.5% of all vesical tumours . The tumour is diagnosed in the seventh decade of life, as documented by most reports. There is a slight male predominance of SCC, as the reported male : female ratio varies from 1.25 : 1 to 1.8 : 1 . The incidence in whites is lower than in blacks even in the presence of the same environmental factors.

PATHOGENESIS

Inflammation from chronic urinary tract irritation, either from bacterial infections, foreign bodies and bladder calculi, or chronic BOO, have been implicated in the pathogenesis of SCC. Many of these factors are present in patients with SCI and long term indwelling catheters.The combined data suggest an incidence of 10% for SCC of the bladder in patients with a catheter indwelling for≥10 years. Other studies have documented a 16–28 times greater risk for SCC of the bladder in paraplegics.A case of invasive SCC of the bladder after intravesical immunotherapy with BCG in a patient with pre-existing squamous dysplasia of the bladder was reported . There have also been eight reports of cyclophosphamide induced SCC of the bladder.

Several authors suggested an association between SCC and long-standing leukoplakia and keratinizing squamous metaplasia . Vitamin A deficiency may be important in SCC .Several studies have addressed the possible role of high-risk HPV in human bladder

cancer, with conflicting results. Complex karyotypes have been recently described in SCC of the bladder originating from primary TCC. Many of the same aberrations described in TCC, e.g. monosomy 9, trisomy 7, and rearrangement of chromosomes 3, 8, 10, 13 and 17, have been detected in SCC .

CLINICO PATHOLOGICAL FEATURES

Haematuria is the principal symptom, in 63–100% of patients, with irritative bladder symptoms in 33–67%. In 35% there is weight loss, back or pelvic pain or frank obstructive symptoms, all of which are suggestive of advanced disease . A UTI is present in 93% of patients at the time of diagnosis.

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 L.N involvement . 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 co variates . 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 . 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 . Death occurs from locoregional progression as a result of ureteric or bladder neck obstruction and kidney failure . These complications highlight the importance of local control and of exploring other therapeutic options to reduce the incidence of pelvic recurrence .

Molecular Biomarkers

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 . 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 . 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 Early Detection

The ultimate solution to the problem lies in its prevention. All efforts should be made to keep patients with SCI free of catheterization, not only to avoid SCC but also to avoid chronic infection, urethral strictures, stone disease

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 off or 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% .Psoriasin, a calcium-binding protein, is expressed largely by stratified squamous epithelia and is externalized to the urine of patients with bladder SCC. Celis*et al.*showed that psoriasin is a potential marker for the noninvasive early detection and follow-up of patients with SCC. Other different biomarkers, e.g. SCC antigen, bcl-2and P53 oncoproteins, may have a possible role in the early diagnosis of SCC .Other biomarkers, including Fork head box protein P3 (Foxp3), may allow the early diagnosis of squamous differentiation and SCC.

At cystoscopy most tumours are solitary,extensive and associated with leukoplakia. The sites occupied by the tumour are variable but there is a predilection for the trigone and lateral walls. Tumours are predominantly ulcerating and infiltrating but rarely fungating. The tumour may occupy a diverticulum and may also be associated with bladder stone .Interestingly, SCC has a low incidence of distant metastasis, at 8–10% ; despite this the prognosis of SCC of the bladder is discouraging, as most patients die after failure of locoregional control. About 90% of the deaths from SCC are caused by locoregional recurrence within 3 years. Distant metastasis is much more often the cause of death in patients with TCC than in patients with SCC.

Treatment Discussion.

At this time, RC(Radical Cystectomy) 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.RC and urinary diversion is the standard treatment of SCC of the urinary bladder. There is a general consensus egarding the necessity for radical surgical treatment, as it allows disease control and better survival than partial cystectomy, radiotherapy, and chemotherapy.

Richie et al. 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.To date, RC with lymphadenectomy is still the 'gold standard' treatment .

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.

Radiation Therapy

Radiation as a primary therapy has previously been associated with poor outcomes . However, it appears to provide some benefit as a preoperative therapy prior to RC. Prospective randomised studies in BSCC have suggested that treatment with preoperative radiotherapy improves disease-free survival (DFS) over RC alone .Adjuvant radiotherapy has historically been associated with serious side-effects including intestinal obstruction and urinary fistulae.

Radiotherapy with concomitant chemotherapy may also function as a useful alternative for unresectable bladder tumours or in cases where bladder preservation is desired .

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 MVAC(methotrexate, vinblastine, doxorubicin and cisplatin)was ineffective in patients with non-TCC.

Galsky et al. 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 . 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.

Immunotherapy

Immunotherapy represents a promising adjunct to conventionalRC for SCC treatment. Intra vesical 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 . Recent studies in TCC have also explored potential immunotherapeutic uses in targeting the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PDL1) axis. PD-1/PD-L1 pathway blockade by antibody appears to reduce T-cell proliferation and Th1 responses . PD-L1 is expressed on activated T-cells and is upregulated in TCC. Immune check point inhibitors have demonstrated activity in metastatic urothelial carcinoma. A new PD-L1 agent atezolizumab showed durable activity and an objective response rate of 26% in platinum-refractory metastatic TCC.

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 NBSCC. Due to rarity of the disease, there is a lack of Level I evidence guiding management of SCC. RC(Radical Cystctomy) 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 personalized medicine.

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