Review

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Squamous Cell Carcinoma of Bladder

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Abstract

Squamous cell carcinoma (SCC) of the bladder is a malignant neoplasm of a pure squamous phenotype originating from the bladder urothelium. SCC of the bladder is a relatively rare tumor with no specific diagnostic test. The diagnosis is usually made at an advanced stage; therefore, the prognosis is poor and most cases result in mortality. Inflammation and infection leading to the metaplasia of epithelial cells are implicated in its etiology. SCC of the bladder is divided into two groups depending on whether it is due to bilharzial infections, and these two groups have different epidemiological, pathogenetic and clinicopathological features. SCC of the bladder accounts for the vast majority (approximately 75%) of bladder cancers in areas where Schistosoma haematobium infection is endemic. The European Association of Urology guidelines classify bladder cancer with any variant histology as high-risk bladder cancer. Because of the rarity and heterogeneity of non-urothelial tumors, treatments described are mostly based on retrospective series and small studies. Radical cystectomy is recommended as the first treatment in patients presenting with non-metastatic bladder SCC. Neoadjuvant radiation therapy (RT) is considered to play a role in schistosomal bladder cancer. However, there are not enough high-quality studies to indicate the role of RT or chemotherapy as adjuvant therapy. Due to the rarity of the disease, there are also no high-evidence guidelines for managing SCC. There is a need for further high-volume and prospective studies to review literature data and developments.

Keywords: Bladder tumor, squamous cell carcinoma, urothelial carcinoma

Introduction

In both men and women he most common genitourinary malignancy is bladder cancer. It is broadly classified as urothelial (98%) and non-urothelial (2%) (1). Although the pathogenesis of non-urothelial bladder cancer has not yet been fully elucidated, the main cause is deemed inflammation and infection leading to the metaplasia of epithelial cells. It constitutes less than 5% of all bladder tumors (1). Approximately 90% of non-urothelial bladder cancers are of epithelial origin, and epithelium-derived bladder cancer cases include small-cell carcinoma (1%), adenocarcinoma (2%) and squamous cell carcinoma (SCC) (3%) (2). Non-epithelial tumors include sarcoma, carcinosarcoma, paraganglioma, melanoma, and lymphoma (1).

Patients with non-urothelial bladder cancer typically present with painless hematuria (macroscopic or microscopic) to urothelial carcinoma, but irritative voiding symptoms (dysuria frequency and urgency) may also be the first sign (3). It has been reported that up to 93% of patients have a urinary tract infection (UTI) at the time of diagnosis (4). This may support the fact that non-urothelial bladder cancer develops in response to chronic infection. In all patients with suspected bladder neoplasms, cystoscopy is the gold standard diagnostic evaluation, and cystoscopic biopsy usually provides tissue for a definitive diagnosis.

Non-urothelial tumors are considered more likely to have invaded muscles at the time of diagnosis than urothelial cancers. Surgical pathological staging is usually an advanced stage at the time of diagnosis. Therefore, bladder cancer with variant histology is reported to have a worse prognosis and survival than the urothelial carcinoma of the bladder, which can be detected at a later stage (5,6,7,8,9). Most patients die within three years, and the five-year survival rate is 33-48% (10).

Pathological Characteristics

The pathogenesis of non-urothelial bladder cancer has not yet been fully elucidated. Both metaplasia and chronic infection are thought to play important roles in tumorigenesis. Another hypothesis includes the formation of non-urothelial bladder cancer from tumor-exposed and pre-developed urothelial carcinomas (transitional cell carcinomas) and metaplasia from multipotent stem cells in the bladder (11).

Non-urothelial bladder cancer develops in response to chronic infection and inflammation, which can lead to the development of tissue metaplasia, leukoplakia and squamous epithelium, or mucinous and glandular epithelium; however, factors leading to neoplastic transformation are unknown. SCC is often affiliated with squamous metaplasia and can be seen in 16-28% of patients with leukoplakia (12). Keratinized squamous metaplasia

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has been identified in most SCC cases, but it can also present as a normal histological variation in female patients. There is insufficient evidence concerning squamous metaplasia being a premalignant finding, and aggressive surgical treatment is not recommended (12,13,14).

Chronic UTIs are associated with both non-schistosomal and schistosomal bladder cancers. Infection may contribute to bladder cancer through multiple mechanisms. Predisposition to metaplasia constitutes the first step for carcinogenesis. Nitrosamines, which are the metabolites of Gram-negative bacteria, such as *Proteus mirabilis* and *Escherichia coli*, are highly carcinogenic for the bladder. Carcinogenesis occurs through DNA appendage formation and possibly other mechanisms. Reactive oxygen species produced by inflammatory cells responding to infection lead to DNA damage and activate other carcinogens (15,16,17,18,19,20).

SCC of the bladder originates from the urothelium and is characterized by a pure squamous cell phenotype. Concerning pathological findings, most SCCs are necrotic, bulky, polypoid, solid masses that fill the bladder lumen. The presence of necrotic material and keratin residues on the surface is typical. It usually involves the trigone region of the bladder, but it can occur in any region of the bladder, including the diverticula, as well as being locally observed in the ureter or urethra (21).

SCC is uncommonly non-muscle invasive, with early-stage (Ta and T1) tumors being rarely reported. In a case series of patients with SCC, T3 lesions (perivesical fat invasion) accounted for 60% of all cases, while only 2% were T1 (14). In the population-based Surveillance, Epidemiology, and End Results (SEER) program, which included 614 patients with SCC, 42.3% of the patients had T3 cancer and 42.5% had a high histological grade (22). In contrast, bilharzial SCCs are mostly well-differentiated tumors, although they are at advanced stages (23). SCC tumors also tend to show low rates of lymphovascular invasion (LVI) and lymph node (LN) metastases (24).

SCC of the bladder is morphologically indistinguishable from that of other regions. The invasive component may show good differentiation with keratinized squamous cell islands, minimal nuclear pleomorphism and prominent intercellular bridges. Poorly differentiated tumors are characterized by marked only focal squamous differentiation and nuclear pleomorphism. The presence of keratinized squamous metaplasia in the adjacent flat epithelium supports the presence of SCC (25).

Epidemiology and Risk Factors

SCC of the bladder is divided into two groups depending on whether it is due to bilharzial infections, and these two groups have different epidemiological, pathogenetic and clinicopathological features (21). SCC of the bladder accounts for the vast majority (approximately 75%) of bladder cancers in areas where Schistosoma haematobium infection is endemic, and it is usually diagnosed in the fifth decade of life in East Africa and the Middle East, where the disease is endemic. The incidence of bilharzial SCC due to the chronic Schistosoma haematobium infection has been reported as 58.8-80.7% in North African countries (26). Non-bilharzial SCC usually occurs in the seventh decade of life and constitutes 3 to 5% of bladder cancers in Europe and North America (4). The male/female ratio has been reported as 4-5:1 for the incidence of bilharzial SCC and 1.3-1.8:1 for that of non-bilharzial SCC (27).

In addition to the schistosomal infection, chronic or recurrent UTIs, previous intravesical Bacillus Calmette-Guerin therapy, pelvic radiation therapy (RT), bladder stones, and prolonged exposure to cyclophosphamide, especially when complicated by hemorrhagic cystitis, have been shown to be among the reported risk factors associated with the development of SCC (1,28,29,30).

In 1989, Brenner et al. (31) described a patient with the previously documented urothelial squamous dysplasia in whom an invasive SCC of the bladder without any transitional cell carcinomatous elements developed one and one-half years after successful eradication of carcinoma *in situ* with intravesical BCG. They drew particular attention to the need for careful evaluation before initiating BCG therapy in a patient with known squamous metaplasia dysplasia or other factors known to predispose to SCC of the bladder (31).

It has been reported that tobacco consumption is an important risk factor for bladder cancer in both SCC and urothelial carcinoma. (23). Although the risk of SCC has also been associated with smoking (32,33), an observational study with a long-term follow-up observed that the incidence of pure SCC was higher in females and had a lower rate of smoking history compared to those with urothelial carcinoma (34).

Several studies have reported that chronic indwelling catheters are associated with an increased risk of SCC, although this relationship remains controversial. Older studies indicate that the incidence of SCC is 10% in patients with indwelling catheters for over 10 years, and the risk of SCC increases 16 to 28 times in patients with paraplegia (35,36). A large study of 43,561 patients with spinal cord injuries (SCI) from Central Europe found no significant difference in bladder cancer risk between these patients and the general population. In this study, bladder cancer developed in 48 patients (0.11%). The data of 8 female and 29 male patients were complete and the mean age of the patients was 53.3 years. As bladder management, reflex voiding was used in 18 patients, intermittent catheterization in 12 patients, and indwelling catheters in 7 patients. They were suggested that the link to bladder cancer was primarily related to indwelling catheters, UTIs, and exposure to carcinogens (37). In another study conducted on 1334 patients with SCI, the age-standardized incidence of invasive bladder cancer was not statistically different from the general population. Also in this study, half of the patients were treated with a chronic indwelling urethral or suprapubic catheter, whereas 35% used intermittent self-catheterization and 15% used one of the alternative voiding methods: abdominal straining, reflex voiding, or urinary diversion (38). The planning of these investigations and the rates of SCC and adenocarcinoma in these individuals may have prevented statistically significant results. However, the incidence of muscle invasion was found to be high in individuals with neurogenic bladder, and researchers suggested that intermittent catheterization should be preferred instead of indwelling catheters in this patient group. Although periodic screening cystoscopy for individuals with spinal cord injury have been

recommended by some authors, no studies have demonstrated the advantage of screening, possibly because the incidence of cancer in these individuals is extremely low (38,39).

Most studies suggest that the human papillomavirus, which is associated with genitourinary cancer, plays a very limited and controversial role in the pathogenesis of the disease (25,26,40). There are publications reporting that there is usually a squamous differentiation in HPV-influenced bladder carcinomas. It has been reported that the virus may exhibit oncogenic activity in the bladder in cases such as persistent condylomatous infection (41). It has also been reported that bladder SCC developing from patients with persistent condylomas develop on the basis of a condyloma (42). It can also be considered that the presence of persistent chronic infection is an important factor in tumorigenesis.

Clinical Course and Treatment

The European Association of Urology guidelines classify bladder cancer with any variant histology as high-risk bladder cancer (43,44). However, the National Comprehensive Cancer Network guidelines provide more specific information depending on the presence of SCC, adenocarcinoma, and neuroendocrine carcinoma (45). Due to the rarity and heterogeneity of non-urothelial tumors, most described treatments are based on the results of retrospective series and small studies.

Radical cystectomy is recommended as the first treatment in patients presenting with non-metastatic bladder SCC (20). For patients with SCC, schistosomal bladder cancer (regardless of histology), or adenocarcinoma, this treatment is recommended to include LN dissection with radical cystectomy (14,46). However, no guidelines offer specific recommendations concerning potential early cystectomy in stage T1 SCC because to the lack of evidence. It has been observed that radical cystectomy increases cancer-specific survival in patients with stage T1 SCC and neuroendocrine carcinoma (43,14).

Observational and retrospective data support surgical treatment. The analysis of the SEER database including the data of 1,422 patients received between 1988 and 2003 showed that the two-year all-cause mortality rate following cystectomy ranged from 11% (in men with stage I disease) to 72% (in men with stage IV disease) (30). After the data were adjusted for age, sex, race, and baseline therapy, SCC histology was determined to be associated with worse outcomes compared to urothelial bladder cancer. However, a recent analysis of all stage III and stage IV bladder cancer cases in Ontario, Canada reported that SCC had a faster disease course than urothelial carcinoma, whereas the five-year overall survival of SCC was similar to urothelial carcinoma after the data were adjusted for covariates (47).

Preoperative or postoperative chemotherapy (CT) is not recommended for the non-urothelial carcinomas of the renal pelvis, ureter, or bladder since these tumors are less responsive to CT compared to urothelial carcinoma and are excluded in phase III studies (48). There are also no high-quality data reporting the role of CT and/or RT as adjuvant therapy.

In schistosomal bladder cancer, RT may play a role before cystectomy, but it is not part of the standard treatment for other bladder tumors (49,50). Preoperative RT can be considered especially in cases where complete resection cannot be performed owing to the suspicion of locally advanced disease. Approximately 90% of mortality in SCC is due to local pelvic recurrence (mostly bladder-urethral anastomosis or ureter). Distant metastasis is rarely observed, at a rate of 8-10% (21).

The tendency for locally high recurrence rates of SCC of the bladder following radical cystectomy suggests that postoperative or preoperative RT with or without radiosensitizing CT can be considered an option. Many retrospective case series have reported possible benefits of neoadjuvant RT or adjuvant (51,52,53,54). In a study conducted with patients with bilharzial SCC, it was determined that the disease-free survival rate was 48% in patients who received adjuvant RT compared with 29% in those that did not receive this therapy (55). However, these results may not be valid for non-schistosomal SCC (49).

Postoperative RT is a viable alternative for patients with persistent locally advanced SCC who are unsuitable or unwilling to undergo adjuvant CT after radical cystectomy. Recent data suggest that this can also be recommended for patients with positive surgical margins (56). The preliminary results of a randomized phase III study of 123 patients with locally advanced disease after radical cystectomy (51% with urothelial carcinoma and 49% with SCC or other carcinoma) indicated that postoperative RT improved local control compared to adjuvant CT (two-year recurrence-free survival: 69% vs 92%, hazard ratio: 0.28) (57). Distant metastasis-free survival, disease-free survival, and overall survival were similar between the two treatment groups. The subgroup analysis of the patients with urothelial carcinoma provided similar results (58).

In patients with unresectable locally advanced bladder SCC (as in head, neck, anus and cervix SCC), RT together with radiosensitizing CT is a treatment can be considered, particularly since the tumor has a locally aggressive course. However, there are only limited prospective data on disease management.

Information from the Phase III study BC2001 shows that mitomycin C and fluorouracil given concomitantly with RT are more effective in local control and survival in patients with muscle-invasive bladder cancer compared to RT alone (59). In that study, only 2.7% of the patients had adenocarcinoma or SCC, and no difference was found when the results were compared with urothelial cancer. A similar treatment regimen in SCC of the anus, which is not suitable for platinum-containing CT, presents as an effective and easily tolerated protocol (60,61). Therefore, it is also a possible treatment option in patients with bladder SCC.

Studies support the idea that SCC tends to be at a locally advanced or worse stage at the time of diagnosis and it is relatively resistant to CT regimens used for metastatic urothelial carcinoma (34,46,62,63). Considering these findings, there is a need for more prospective clinical studies.

The promising results of T-cell checkpoint immunotherapy treatments using pembrolizumab or atezolizumab in patients, who treated previously with platinum-based regimens for advanced urothelial carcinoma, as well as results obtained from immunotherapy in patients with lung, head, and neck SCC justify the inclusion of patients with SCC of the bladder in clinical trials (64). Atezolizumab, a PDL-1 (Programmed Death-

Ligand 1) agent, showed sustained activity and an objective response rate of 26% in platinum-resistant metastatic urothelial carcinoma (65). Although there are no data to support the use of immunotherapy in SCC of the bladder, it appears that clinical benefits may guide future treatment protocols.

The scarcity of clinical studies on metastatic diseases suggests that metastatic urothelial cancer treatment regimens can be considered. In a Phase II study, in which both 43 patients with urothelial cancer and 6 patients with bladder SCC were successfully treated with good outcomes, suggests that the combination of carboplatin, gemcitabine and paclitaxel can be preferred for treating these patients (66).

Some molecular biomarkers have also been investigated to predict oncological outcomes. Fibroblast growth factor 2 (FGF-2) overexpression has been reported to be associated with the aggressive pathological features of including LVI, LN involvement, and SCC, as well as worse overall outcomes following radical cystectomy. Additionally, it has been observed that changes in cyclooxygenase 2 (COX-2) can predict poor outcomes (23). It has also been suggested that a panel of five biomarkers, namely COX-2, p53, Bax, FGF-2, and epidermal growth factor receptor can predict outcomes after cystectomy (67). Lastly, the expression of the human epidermal growth factor receptor 2 oncoprotein has been reported to be at high levels in SCC tumors (68). It is considered that these biomarkers can guide the determination of optimal treatment approaches.

Conclusion

Due to the rarity of SCC of the bladder, there is a lack of level I evidence guidelines for managing the disease. There is a need for high-volume and prospective studies on all work and developments in this area. This will help develop more accurate and effective guidelines for multimodal treatment approaches.

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