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Squamous Cell Carcinoma of Bladder

Ferhat Cetin and Özer Birge

Abstract

Urinary bladder tumors are the second most common malignancy of the urinary system. In 2012, the global age-standardized incidence rate (per 100,000 person/years) was reported as 9.0 for men and 2.2 for women. Usually, bladder cancers are seen in middle and old-aged people. In the United States, the average age for getting a diagnosis was 72 years. It was reported that 90% of newly diagnosed patients were above 60 years and rarely below 35 years. Bladder tumors relapse approximately 50–75% within 5 years after diagnosis, and progressions occur in 10–20% of them. While the five-year survival rate of organ-confined disease is 94%, the survival rates of locally invasive and metastatic tumors varied between 6 and 49%. Most of the bladder urothelial carcinomas diagnosed in patients under 40 years of age are low-grade and stage I, and the 5-year survival rate is around 97%.

Keywords: bladder, urinary system, squamous cell carcinoma

1. Introduction

Bladder cancer is the most frequent genitourinary malignancy in both men and women. They are divided into two groups—urothelial and nonurothelial.

2. Anatomy

The bladder is located in the midline just behind the pubic bone. The bladder is separated from the pubic bone by the retropubic space, also known as the Retzius space, including the Santorini venous plexus. The symphysis pubis, laterally the pelvic side-walls, posteriorly and inferiorly the lower uterine segment, anterior cervix, and vagina are the bladder's boundaries. The obliterated umbilical artery and urachus correspond to the upper border of the bladder. The urachus connects the developing bladder to the umbilicus in the fetus. After birth, the urachus curves into the median umbilical ligament, which connects the apex of the bladder to the anterior abdominal wall. Sometimes, the urachus remains patent. The bladder dome is located next to the anterior abdominal wall's parietal peritoneum. The bladder is pushed into the vesicouterine space by the peritoneum below. The bladder's thick parts are retroperitoneal. The bladder is an organ that has the ability to expand. When empty, it has the shape of a pyramid. The tip points to the pubic bone. It becomes a sphere when it is full, with a capacity of about 400–500 cc

in a healthy adult individual, and it changes from a pelvic to an abdominal organ in this state. When the dome is completely filled, the dome's structure becomes thinner than the dome's other parts. As a result, emptying the bladder with the aid of a catheter before beginning pelvic surgery can assist in preventing bladder injuries. The upper dome and lower floor are present in the bladder. The bladder floor, which comprises the trigone and detrusor ring, is located directly on the anterior wall of the vagina. Thickening of the detrusor muscle is a thickening that does not change directly with bladder filling. The area between the two ureteral orifices and the internal urethral meatus is known as the bladder trigone. The two ureteral orifices and the internal urethral meatus are 3 cm apart. The intraurethral ridge is a rise in the trigone between the ureteral orifices [1].

The bladder wall is made up of four layers:

a. Urothelium

The urothelium is the bladder's innermost layer, consisting of transitional epithelial cells. Bladder cancer originates in the urothelial layer.

b. Lamina propria

A thin basement membrane separates the lamina propria (subepithelial connective tissue) from the urothelium. This layer consists of rich connective tissue containing vascular and neuronal structures. Thin, smooth muscle fibers may be present in the middle of this layer, partially or as a separate layer, along with the vascular plexus. This area is also called muscular mucosa.

c. Muscularis propria

The muscularis propria (detrusor muscle) are thick, interlocking, irregular muscle bundles surrounding the lamina propria. When the bladder contracts, the detrusor muscle's plexiform structure is ideal for reducing all lumen dimensions. Small muscle fibers in the lamina propria (muscularis mucosa) described above can be confused with this layer in small biopsies, potentially leading to incorrect tumor staging. The lamina propria and/or muscularis propria may include adipose tissue. Therefore, the presence of a tumor in adipose tissue does not always indicate extravesical spread.

d. Serosa (adventitia)

It is the name for the perivesical adipose tissue outside the muscularis propria [1, 2].

The superior and inferior vesical arteries, which arise from the anterior branch of the internal iliac artery, give blood to the bladder. The pelvic and hypogastric nerve plexuses' parasympathetic and sympathetic autonomic fibers supply bladder innervation [1].

3. Epidemiology

Nonurothelial bladder cancer makes up fewer than 5% of all bladder tumors [3]. About 90% of nonurothelial bladder cancers are epithelial in origin. Most of them

are squamous cell carcinomas; other rare types are adenocarcinomas and small cell carcinomas. Non-epithelial tumors include sarcomas, carcinosarcomas, paragangliomas, melanomas, and lymphomas.

4. Pathogenesis and risk factors

The pathogenesis of nonurothelial bladder cancers is not fully understood. The presence of chronic infection and metaplasia development are believed to be crucial factors in tumorigenesis. Alternative hypotheses include the development of nonurothelial bladder cancers from pre-existing urothelial (transitional cell) carcinomas undergoing metaplasia [4] and tumor growth from multipotent stem cells in the bladder.

Chronic infection and inflammation cause tissue metaplasia, resulting in the development of either squamous epithelium and leukoplakia or mucous and glandular epithelium. The factors that cause neoplastic transformation, on the other hand, are unknown.

- Squamous cell carcinomas are frequently associated with squamous metaplasia and occur in 16–28% of leukoplakia patients [5, 6].
- Adenocarcinoma has been linked to two models of metaplasia. Invagination of hyperplastic epithelial buds into the lamina propria causes cystitis cystica, which can progress to metaplasia and cystitis glandularis and is linked to vesical adenocarcinoma. Hyperplasia of epithelial mother cells is shown in a second pattern, but there is no invagination into the lamina propria.

Both non-schistosomal and schistosomal bladder cancer are associated with chronic urinary tract infections (UTIs). Infection may play a role in the development of bladder cancer through a variety of mechanisms, including:

- Predisposition to metaplasia is the first step in carcinogenesis.
- Gram-negative bacteria, such as *Escherichia coli* and *Proteus mirabilis*, create nitrosamines, which are extremely carcinogenic metabolites. Carcinogenesis results from the formation of DNA adducts and possibly by other mechanisms [7–12].
- Inflammatory cells' production of reactive oxygen species in response to infection causes DNA damage and the activation of additional carcinogens.

5. Clinical presentation

Patients with nonurothelial bladder cancer often have painless hematuria (visible or microscopic), but irritating urination symptoms (frequency, urgency, and dysuria) may be the initial indicator, similar to urothelial carcinomas.

Nonurothelial bladder cancers have a variety of less common presentations, including:

- Mucusuria has been described in bladder adenocarcinomas and is more common in urachal adenocarcinomas than in non-urachal adenocarcinomas.
- The presence of an abdominal mass is more common in urachal adenocarcinoma compared to in non-urachal adenocarcinoma.

6. Diagnostic evaluation

Cystoscopy is the gold standard for diagnosing a patient with a suspected bladder neoplasm, and cystoscopic biopsy typically gives tissue for a definite diagnosis. Compared to urothelial cancers, non-urothelial tumors are more likely to be muscle-invasive at diagnosis and more likely to be staged at the time of surgery because precise pathological staging is available. Therefore, as a group, non-urothelial tumors occur at a more advanced stage and contribute to a worse prognosis compared to urothelial cancers [13]. However, an interesting observation is that urachal cancers tend to have a better prognosis at presentation than urothelial cancers at a similar stage (Table 1) [14].

Primary tumor (T)	
T category	T criterion
TX	Primary tumor unknown
T0	No evidence of primary tumor
Ta	Noninvasive papillary tumor
Tis	Carcinoma <i>in situ</i> : “Flat tumor”
T1	Invasive to the lamina propria
T2	Invasive into the muscularis propria
pT2a	Invasive into the superficial muscularis propria
pT2b	Invasive into the deep muscularis propria
T3	Invasive perivesical adipose tissue
pT3a	Microscopic
pT3b	Macroscopic
T4	Extravesical tumor invasive of either the prostatic stroma, seminal vesicle, uterus, vagina, pelvic wall, or abdominal wall
T4a	Extravesical tumor invading the prostatic stroma, seminal vesicle, uterus, and vagina
T4b	Extravesical tumor of the pelvic wall, invasive into the abdominal wall
Regional lymph nodes (N)	
N category	N criterion
NX	Lymph node metastasis unknown
N0	No lymph node metastases
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal iliac, external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastases in the true pelvis (perivesical, obturator, internal iliac, external iliac, or sacral lymph nodes)
N3	Common iliac lymph node metastasis
Distant metastasis (M)	
M category	M criterion
M0	No distant metastases
M1	There is distant metastasis
M1a	Distant metastasis limited beyond the common iliac

Distant metastasis (M)			
M category	M criterion		
M1b	Presence of distant metastases without lymph node metastasis		
Prognostic staging groups			
When T is like this	When N is like this	When M is like this	The staging group goes like this
Ta	N0	M0	0a
Tis	N0	M0	0is
T1	N0	M0	I
T2a	N0	M0	II
T2b	N0	M0	II
T3a, T3b, T4a	N0	M0	IIIA
T1-T4a	N1	M0	IIIA
T1-T4a	N2, N3	M0	IIIB
T4b	Any N	M0	IVA
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

Table 1.
AJCC cancer staging 2017.

7. Overview of the treatment approach

The treatment of nonurothelial bladder tumors is mainly based on retrospective series and small trials due to their rarity and heterogeneity. As a result, the approach to patients with urothelial bladder cancer is frequently used to estimate treatment.

Cystectomy is the primary treatment for patients with localized illness. This should include a lymph node dissection with radical cystectomy for individuals with squamous carcinoma, adenocarcinoma, or schistosomal bladder cancer (regardless of histology).

Nonurothelial carcinomas of the bladder, ureter, or renal pelvis are not recommended for preoperative or postoperative chemotherapy because they are less responsive to chemotherapy than urothelial carcinomas and were not included in the phase III trials.

Although radiation therapy (RT) before cystectomy may play a role in schistosomal bladder cancer, it is not a standard treatment approach for other bladder tumors [15, 16]. There are no high-quality data on the role of chemotherapy and/or RT as adjuvant therapy.

Palliative care, RT, or chemotherapy are options for patients with advanced nonurothelial bladder cancer who are not candidates for surgery, including those with metastatic disease. Such patients should participate in clinical trials whenever possible. However, a trial of chemotherapy is reasonable in patients who are candidates for chemotherapy and are in good performance status. When deciding on treatment, it should be kept in mind that there are no prospective data that provide information on the benefits of treatment compared with the risks associated with treatment.

Because trials for certain groups of nonurothelial carcinomas are not common, these patients are often candidates for early phase clinical trials and “basket studies”

that allow enrollment of tumors with specific mutations that are considered “vulnerable” to the drug being offered. According to case reports, nonurothelial malignancies may react to targeted agents found by molecular profiling techniques, such as next-generation sequencing [17, 18]. Patients with potentially actionable mutations in their tumors should be included in clinical studies that capture molecular, response, and outcome data prospectively whenever possible [19, 20].

8. Squamous cell carcinoma

In North America and Europe, squamous cell carcinoma accounts for 3 to 5% of bladder cancers and 75% of bladder cancers in areas where *Schistosoma haematobium* infection is endemic.

Risk factors associated with the development of squamous cell carcinoma include chronic or recurrent urinary tract infections (UTIs), bladder stones, pelvic radiotherapy (RT), previous intravesical Bacillus Calmette-Guerin (BCG) therapy, and prolonged cyclophosphamide treatment, especially when complicated by hemorrhagic cystitis, in addition to schistosome infection [3]. Although smoking raises the risk of squamous cell carcinoma [21, 22], an observational study with long-term follow-up reveals that patients with pure squamous cell carcinoma are more likely to be female and have never smoked than patients with urothelial carcinoma [23]. In some studies, chronic indwelling catheters have also been associated with an increased risk of squamous cell carcinoma, while the relationship is controversial.

Although the design of these studies and the prevalence of squamous cell cancer and adenocarcinoma in these patients may have precluded a statistically significant result, two large population-based studies in patients with spinal cord injury did not find an increased risk of bladder cancer [24, 25]. However, muscle invasion was more common in bladder cancer detected in patients with neurogenic bladder, and researchers preferred intermittent catheterization to indwelling catheters [25]. Although some investigators have recommended regular screening cystoscopies for patients with spinal cord injury, no studies have proved a benefit of screening, perhaps because of the extremely low incidence of cancer in these patients [26, 27].

Surgery is the primary treatment for squamous cell carcinoma. Preoperative RT is appropriate, especially when complete resection is possible due to suspected locally advanced disease.

The role of surgery is supported by observational and retrospective data. In a study of 1422 patients diagnosed with bladder cancer between 1988 and 2003, 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, according to the results of a Surveillance, Epidemiology, and Final Results (SEER) database analysis [28]. Squamous cell carcinoma histology was statistically associated with worse prognosis outcomes than urothelial bladder cancer histology when age, gender, race, and starting treatment were classified equally for both groups.

The tendency for local recurrence of bladder squamous cell carcinoma after radical cystectomy provides the rationale for preoperative or postoperative RT with or without radiosensitizing chemotherapy. Unfortunately, due to the small number of patients included, bias in patient selection, and treatment heterogeneity, the quality of available data is limited.

Because of the risk of intestinal toxicity and the difficulty of determining an appropriate RT treatment region after bladder removal, preoperative RT is preferable

to postoperative therapy in such cases. However, several retrospective case series have indicated potential benefits of adjuvant or neoadjuvant RT [29–32]. There has only been one prospective study on schistosomiasis infection, and the results may not apply to non-schistosomal squamous cell carcinoma.

Postoperative RT is a reasonable option for patients with locally progressed squamous cell bladder cancer following radical cystectomy unsuitable for or refusing adjuvant chemotherapy. New evidence supports its usage in patients with surgical margins that are positive [33]. In preliminary results of a randomized phase III trial of 123 patients with locally advanced bladder cancer (51% with urothelial carcinoma and 49% with squamous cell carcinoma or other carcinomas) after radical cystectomy versus adjuvant chemotherapy, RT improved local control (two-year local disease-free survival 92% vs. 69%, HR 0.28, 95% CI 0.10–0.82) [34]. The two treatment arms had similar disease-free survival, distant metastasis-free survival, and overall survival. Similar results were seen in a subgroup of patients with urothelial carcinoma [35].

Radiation combined with radiosensitizing chemotherapy (as is done for squamous cell carcinoma of the head and neck, anus, and uterine cervix) is a reasonable approach for patients with locally advanced, unresectable squamous cell carcinoma of the bladder, especially since these tumors tend to be locally aggressive. However, there are few forward-looking data to guide treatment.

Data from the phase III study BC2001 demonstrate efficacy for fluorouracil and mitomycin given with RT compared to RT alone in patients with high-grade muscular-invasive bladder cancer, who tend to have improved local and regional control and better survival [36]. Only 2.7% of patients in this trial had adenocarcinoma or squamous cell carcinoma, and there was no difference in outcomes compared to urothelial cancer. In patients with squamous cell carcinoma of the anus, a very comparable regimen is effective and well-tolerated; thus, extrapolation to squamous cell cancer of the bladder may be reasonable, especially in patients who are poor candidates for platinum-containing chemotherapy [37, 38].

Limited data suggest that squamous cell carcinoma tends to be locally advanced or worse at diagnosis and relatively resistant to chemotherapies used for metastatic urothelial carcinoma [23, 39–41]. We prefer that these patients participate in a prospective clinical trial in view of these results. The encouraging results of immunotherapy with T-cell checkpoint inhibitors using atezolizumab or pembrolizumab in advanced urothelial carcinoma previously treated with platinum-based therapy [42, 43], as well as the results of immunotherapy in patients with squamous cell carcinoma of the lung and head and neck tumors, support the inclusion of patients with squamous cell carcinoma of the urinary bladder in clinical trials, and we, therefore, continue to seek such trials for these patients [42, 43].

Treatment regimens used to treat metastatic urothelial cancer could be tried in the absence of a clinical trial. Based on phase II trial data in which six patients with bladder squamous cell carcinoma were treated with satisfactory results, similar to urothelial cancer patients in the same study, we recommend the combination of carboplatin, gemcitabine, and paclitaxel [44]. The experience from this trial is reproducible in our clinical practice for advanced squamous cell carcinoma of the bladder.

9. Prognosis

It is unclear whether nonurothelial bladder cancers have a worse prognosis, especially after controlling for stage and grade. After controlling for gender, stage, and

grade, a multi-institutional study of 1131 consecutive patients (including 1042 with urothelial carcinoma and 89 with nonurothelial bladder cancer) found no differences in five-year survival following radical cystectomy [45].

10. Conclusion

Urothelial and nonurothelial bladder cancers are the two types of bladder cancer. Nonurothelial bladder cancers are further divided into epithelial and non-epithelial. Squamous cell carcinomas, adenocarcinomas, and small cell (neuroendocrine) tumors are epithelial cancers that account for around 90% of these cancers. Non-epithelial cancers are rare and include sarcomas, carcinosarcomas, paragangliomas, melanomas, and lymphomas. The pathogenesis of nonurothelial bladder cancers is not fully understood. The presence of chronic infection and inflammation, as well as the development of metaplasia, are regarded to be important factors in tumorigenesis. Like urothelial carcinomas, nonurothelial bladder carcinomas often present with hematuria and bladder irritation. Mucusuria has been described in bladder adenocarcinomas and is more common in urachal types than in non-urachal adenocarcinomas. The presence of an abdominal mass may also suggest a diagnosis of adenocarcinoma of the urinary bladder. Infection with *Schistosoma haematobium* is associated with squamous cell carcinoma, urothelial carcinoma, and adenocarcinoma of the bladder. Nonurothelial bladder cancers account for 80% of bladder cancer cases in areas where such infections are endemic. We recommend surgery for most patients with non-metastatic, nonurothelial bladder cancer. Adjuvant therapy does not have a defined role in most of these patients, although some patients may benefit from neoadjuvant or adjuvant radiotherapy, and patients with schistosomal bladder cancer may benefit from adjuvant chemoradiation. We recommend palliative treatment for patients with advanced bladder cancer who are not candidates for surgery. However, a trial of chemotherapy is reasonable in patients who are candidates for chemotherapy and are in good performance status. When deciding on treatment, it should be kept in mind that there are no prospective data that provide information on the benefits of treatment compared with the risks associated with treatment. In patients with non-epithelial, nonurothelial bladder cancer, in the absence of better evidence, we use the most appropriate treatments for these tumor types when they occur elsewhere. However, it is important to ensure that metastatic disease is excluded.

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Conflict of interest

The authors declare no conflict of interest.

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