Original Research Article

Clinical evaluations of oncologic outcomes in patients with non-urothelial bladder cancer

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Abstract

Bladder cancer has the highest recurrence rate of any malignancy. Although most patients with bladder cancer can be treated with organ-sparing therapy, most experience either recurrence or progression, creating a great need for accurate and diligent surveillance. More than 90% of the urinary bladder malignancies are represented by urothelial carcinomas. Trans - uretheral resection of bladder tumor (TURBT) provides the necessary material for histopathological examination as it allows assessment of degree of differentiation, depth of invasion, and other parameters required for diagnosis and prognosis assessment. Hence the present study was planned to evaluate the clinical evaluations of oncologic outcomes in patients with nonurothelial bladder cancer.The present study was planned in the Department of Urology,Hanumant Hospital, Bhavnagar, Gujarat and Kurji Holy Family Hospital, Patna, Bihar, India. The study was performed from the June 2016 to May 2019. The patients diagnosed with bladder cancer and referred to our hospital were enrolled in the present study. All the patients were informed and consents taken. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study. The data generated from the present study concludes that early detection and treatment of new / recurrent cases is required to optimize bladder preservation, reduce patient morbidity and increase quality of life. The incidence of bladder tumors of both urothelial and non-urothelial varieties is significantly lower in patients less than 40 years.

Keywords: urothelial, non-urothelial, bladder cancer, Oncologic Outcomes.

Introduction

Bladder cancer is a common urologic cancer that has the highest recurrence rate of any malignancy. In North America, South America, Europe, and Asia, the most common type is transitional cell carcinoma. Other types include squamous cell carcinoma and adenocarcinomas. Bladder cancer is a common urologic cancer. Almost all bladder cancers originate in the urothelium, which is a 3- to 7-cell mucosal layer within the muscular bladder.

In North America, South America, Europe, and Asia, the most common type of urothelial tumor diagnosed is transitional (urothelial) cell carcinoma (TCC); it constitutes more than 90% of bladder cancers in those regions. TCC can arise anywhere in the urinary tract, including the renal pelvis, ureter, bladder, and urethra, but it is usually found in the urinary bladder.

Carcinoma in situ (CIS) is frequently found in association with high-grade or extensive TCC.

Squamous cell carcinoma (SCC) is the second most common cell type associated with bladder cancer in industrialized countries. In the United States, around 5% of bladder cancers are SCCs. [1] Worldwide, however, SCC is the most common form of non urothelial bladder cancer, accounting for 75% of cases in developing nations. In the United States, the development of SCC is associated with persistent inflammation from long-term indwelling Foley catheters and bladder stones, as well as, possibly, infections. In developing nations, SCC is often associated with bladder infection by Schistosoma haematobium.

Approximately 2% of bladder cancers are adenocarcinomas. Nonurothelial primary bladder tumors are extremely rare and may include small cell carcinoma, carcinosarcoma, primary lymphoma, and sarcoma (see Pathophysiology). Small cell carcinoma of the urinary bladder accounts for only 0.3-0.7% of all bladder tumors. High-grade urothelial carcinomas can also show divergent histologic differentiation, such as squamous, glandular, neuroendocrine, and sarcomatous features.

The clinical course of bladder cancer is marked by a broad spectrum of aggressiveness and risk. Low-grade, superficial bladder cancers have minimal risk of progression to death; however, high-grade non–muscle-invasive cancers frequently progress and muscle-invasive cancers are often lethal. The classic presentation of bladder cancer is painless gross hematuria, which is seen in approximately 80-90% of patients. Physical examination results are often unremarkable. Cystoscopy, cytology, and biopsy when necessary are the principal diagnostic tests. Upon presentation, 55-60% of patients have low-grade, noninvasive disease, which is usually treated conservatively with transurethral resection of bladder tumor (TURBT) and periodic cystoscopy. Intravesical agents may also be given selectively to decrease the frequency of recurrences. The

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remaining patients have high-grade disease, of which 50% is muscle invasive and is typically treated with radical cystectomy or with trimodality therapy (i.e, TURBT followed by concurrent radiation therapy and systemic chemotherapy).

Carcinoma in situ (CIS) is managed by TURBT and instillation of chemotherapeutic or immunotherapeutic agents—most commonly, immunotherapy with bacillus Calmette-Guérin (BCG) vaccine—into the bladder via catheter. These intravesical treatments are not effective in the 20% of patients in whom cancer has invaded the bladder wall muscle; those cases require cystectomy or a combination of radiation therapy and chemotherapy.

The bladder is an extraperitoneal muscular urine reservoir that lies behind the pubis symphysis in the pelvis. At the dome of the bladder lies the median umbilical ligament, a fibrous cord that is anchored to the umbilicus and that represents the obliterated urachus (allantois). The ureters, which transport urine from kidney to bladder, approach the bladder obliquely and posterosuperiorly, entering at the trigone (the area between the interureteric ridge and the bladder neck). The intravesical ureteral orifices are roughly 2-3 cm apart and form the superolateral borders of the trigone. The bladder neck serves as an internal sphincter, which is sacrificed during a radical cystectomy.

In males, the seminal vesicles, vas deferens, ureters, and rectum border the inferoposterior aspect of the bladder. Anterior to the bladder is the space of Retzius, which is composed of fibroadipose tissue and the prevesical fascia. The dome and posterior surface of the bladder are covered by parietal peritoneum, which reflects superiorly to the seminal vesicles and is continuous with the anterior rectal peritoneum. In females, the posterior peritoneal reflection is continuous with the uterus and vagina.

The vascular supply to the bladder arrives primarily via the internal iliac (hypogastric) arteries, branching into the superior, middle, and inferior vesical arteries, which are often recognizable as lateral and posterior pedicles. The arterial supply also arrives via the obturator and inferior gluteal artery and, in females, via the uterine and vaginal arteries. Bladder venous drainage is a rich network that often parallels the named arterial vessels, most of which ultimately drain into the internal iliac vein.

Initial lymphatic drainage from the bladder is primarily into the external iliac, obturator, internal iliac (hypogastric), and common iliac nodes. Following the drainage to these sentinel pelvic regions, spread may continue to the presacral, paracaval, interaortocaval, and para-aortic lymph node chains. Almost all bladder cancers originate in the urothelium, which is a 3- to 7-cell mucosal layer within the muscular bladder. Squamous cell carcinoma of the bladder can involve multiple sites; however, the lateral wall and trigone are more commonly involved by this tumor. All small cell carcinomas of the urinary system identified so far have been located in the urinary bladder, most commonly in the dome and vesical lateral wall. [2]

Bladder cancer is often described as a polyclonal field change defect with frequent recurrences due to a heightened potential for malignant transformation. However, bladder cancer has also been described as resulting from implantation of malignant cells that have migrated from a previously affected site. The latter occurs less often and may account for only a small percentage of cases.

Use of the common term superficial bladder cancer should be discouraged. The term implies a harmless nature, which is misleading in many instances. Because it was used to describe the disparate disorders of low-grade papillary bladder cancer and the markedly more aggressive form, carcinoma in situ (CIS), the World Health Organization (WHO) has recommended it to be abandoned.

In its place, the term non–muscle-invasive bladder cancer should be used and qualified with the appropriate American Joint Committee on Cancer stage (ie, Ta, T1, Tis). Stage T1 cancer invades lamina propria but not the muscle of the bladder. High-grade T1 tumor associated with CIS carries a relatively high risk for disease recurrence and progression (approximately 60%). The WHO classifies bladder cancers as low grade (grades 1 and 2) or high grade (grade 3). Tumors are also classified by growth patterns: papillary (70%), sessile or mixed (20%), and nodular (10%).

Transitional cell carcinoma (TCC) arises from stem cells that are adjacent to the basement membrane of the epithelial surface. Depending on the genetic alterations that occur, these cells may follow different pathways in the expression of their phenotype. The most common molecular biologic pathway for TCCs involves the development of a papillary tumor that projects into the bladder lumen and, if untreated, eventually penetrates the basement membrane, invades the lamina propria, and then continues into the bladder muscle, where it can metastasize. Nearly 90% of transitional cell bladder tumors exhibit this type of behavior. This progression occurs with high-grade cancers only. Low-grade cancers rarely, if ever, progress and are thought to have a distinct molecular pathway, different from the high-grade cancers and CIS. The remaining 10% of TCCs follow a different molecular pathway and are called CIS. This is a flat, noninvasive, high-grade urothelial carcinoma tumor that spreads along the surface of the bladder and, over time, may progress to an invasive form of cancer that behaves the same as invasive TCC. Many urothelial tumors are primarily composed of TCC but contain small areas of squamous differentiation, squamous cell carcinoma (SCC), or adenocarcinoma.

Up to 80% of bladder cancer cases are associated with environmental exposure. Tobacco use is by far the most common cause of bladder cancer in the United States and is increasing in importance in some developing countries. Smoking duration and intensity are directly related to increased risk. [1, 3-4]

The risk of developing bladder carcinoma is 2-6 times greater in smokers than in nonsmokers. This risk appears to be similar between men and women. [5] Nitrosamine, 2-naphthylamine, and 4-aminobiphenyl are possible carcinogenic agents found in cigarette smoke. A number of occupations involve exposure to substances that may increase risk for bladder cancer. Of occupationally related bladder cancer cases, the incidence rate is highest in workers exposed to aromatic amines, while mortality is greatest in those exposed to polycyclic aromatic hydrocarbons and heavy

metals. [6] Numerous occupations associated with diesel exhaust, petroleum products, and solvents (eg, auto work, truck driving, plumbing, leather and apparel work, rubber and metal work) have also been associated with an increased risk of bladder cancer.

Bladder cancer has the highest recurrence rate of any malignancy. Although most patients with bladder cancer can be treated with organ-sparing therapy, most experience either recurrence or progression, creating a great need for accurate and diligent surveillance. More than 90% of the urinary bladder malignancies are represented by urothelial carcinomas. [7] Trans - uretheral resection of bladder tumor (TURBT) provides the necessary material for histopathological examination as it allows assessment of degree of differentiation, depth of invasion, and other parameters required for diagnosis and prognosis assessment. [8] Hence the present study was planned to evaluate the clinical evaluations of oncologic outcomes in patients with nonurothelial bladder cancer in patients treated in two different institutions.

Methodology

The present study was planned in the Department of Urology Hanumant Hospital,Bhavnagar Gujarat and Kurji Holy Family Hospital, Patna, India. The study was performed from the June 2016 to May 2019. The patients diagnose with bladder cancer and refereed to our hospital were enrolled in the present study.

All the patients were informed and consents taken. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria

Data was evaluated for age, gender, clinical symptoms and histopathological characteristics at the time of presentation. A Transurethral resection of the bladder tumor (TURBT) was performed in most of the cases except two cases. Urinary bladder tumor tissue biopsy/ specimen were received by our Histopathology department and subjected to routine histopathology processing. Then tissue sections were studied. The new 2016-based World Health Organization (WHO) and International Society of Urological Pathology (ISUP) classification for Papillary Urothelial neoplasms were used for the pathological grading of the cases studied. [9]

Exclusion criteria

1. Patients with tumors other than urinary bladder neoplasms in the urinary system of both sexes.
2. Patients not willing for management at our cancer centre.

Results & Discussion

There have been a number of comparative studies on urothelial tumors in younger and older age groups. The findings of this study were consistent with those of previously published reports. According to most of the studies, the carcinoma of bladder is a disease of the elderly with marked male predominance. [10-12]

The effect of age on the histopathological findings of bladder tumor is poorly investigated and understood. Maybe prolonged exposure to carcinogens like smoking in older age leads to formation of more malignant varieties. Besides, genetic factors may also play a role in higher incidence of invasive carcinomas in older age. [10]

Table 1:Variables

Variables	Urothelial cell carcinoma	Squamous cell carcinoma	Adenocarcinoma	Sarcoma	Small cell	Signet ring	Spindle cell
No. of Cases	15	6	4	4	2	1	1
Age (years)	58 – 61	45 – 63	52 – 67	49 – 59	51 – 67	51	62
Males	11	6	2	3	2	1	1
Married	15	4	3	3	2	0	0
High grade	12	6	2	2	2	1	1
T-Stage:							
<T2	5	1	1	0	0	0	0
T2	4	1	1	2	1	0	0
T3	5	3	2	1	1	1	1
T4	1	1	0	1	0	0	0
N-Stage:							
N0	10	1	4	1	0	0	0
N+	3	3	0	2	2	1	1
NX	2	2	0	1	0	0	0

T1 carcinoma of the urinary bladder is a heterogeneous disease with potentially aggressive behavior leading to lethality [13]. Indeed, despite sharing many of the genetic and epigenetic factors of muscle-invasive bladder cancer, it is classified as non-muscle invasive. Yet, patients with T1 bladder cancer have an overall mortality of 33% and a cancer-specific mortality of 14% at three years after diagnosis, suggesting that these patients have a high risk of disease progression and, accordingly, require meticulous surgery, endoscopic surveillance and informed clinical decision-making [14].

The variability in the outcomes of patients with T1 bladder cancer is a result of both tumor heterogeneity and pathological staging, as well as inconsistencies in risk

stratification, endoscopic resection and schedules of delivery of BCG [15]. Owing to limitations in clinical staging, patients with T1 bladder cancer are at risk of both under-treatment with use of BCG despite recurrence, and overtreatment with early radical cystectomy. Understanding the pathologic features of T1 bladder cancers and how they impact prognosis and, therefore, could improve risk stratification to align therapy with biological risk and clinical behavior of the individual tumor [16-17]. While novel prognostic features such as variant histology and lymphovascular invasion have been included in the clinical decision-making, more features are needed to improve our prognostic accuracy [17-19].

The present study is the first to perform a comparative survival analysis for multiple histologic variants relative to urothelial carcinoma while controlling for age and other adverse pathologic characteristics. Survival information for patients with rare bladder tumors underrepresented in the literature provided by our study will prove useful in counselling newly diagnosed patients.

Besides AC and small cell carcinoma, the remaining analysed histologic variants were associated with worse OS and DSS following radical cystectomy. The reasons for the worse survival in these patients are certainly multifactorial. First, the tumor biology and natural history of nonurothelial tumors may have more aggressive characteristics and thus portend a poor prognosis. Second, the paucity of published clinical series is in general fragmented with series limited to institutional series makes optimal treatment regimens and timely management of these tumors difficult.

Conclusion

The data generated from the present study concludes that early detection and treatment of new / recurrent cases is required to optimize bladder preservation, reduce patient morbidity and increase quality of life. The incidence of bladder tumors of both urothelial and non-urothelial varieties is significantly lower in patients less than 40 years.

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