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Original Research Article

A Hospital Based Oncologic Outcomes Assessment in Patients with Nonurothelial Bladder Cancer

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Abstract

Aim: The objective of the present study was to oncologic outcomes in patients with nonurothelial bladder cancer in Bihar region.

Methods: The present study was conducted in the Department of medical oncology, IGIMS, Patna, Bihar, India. The patients diagnose with bladder cancer and refereed to our hospital were enrolled in the present study.

Results: Majority of the cases were Urothelial cell carcinoma (50%) followed by Squamous cell carcinoma (16.66%). Most of the patients in the study were married male. The maximum number of patients fell under T1 stage and N0 stage. The univariable hazard ratio (HR) and 3-year and median OS and DSS by histologic subtype. With the exception of AC, all nonurothelial bladder cancers have a worse 3-year OS and DSS when compared to UCC. The worst DSS was demonstrated in small cell histology with 3-year survival probabilities of 41.6%.

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.

Keywords: non-urothelial bladder cancer, radical cystectomy, chemotherapy

Introduction

Bladder cancer accounts for over 70,000 new cancer diagnoses per year in the United States, with pure urothelial cell carcinoma (UCC) comprising approximately 90%–95% of these cases.

[1−3] The remaining 5%–10% of bladder cancers consist of pure non-urothelial histologies or mixed urothelial and non-urothelial histologies, and these are generally associated with a worse prognosis compared to urothelial cell bladder carcinoma.[4]

In 90-95% of patients, BC is of urothelial origin [5], known as transitional cell carcinoma (TCC), and the rest small percentage is composed of non-urothelial BCs (NUBCs). Like TCC, these uncommon cancers exhibit geographical variations, e.g., regions with endemic schistosomal cystitis show a higher incidence of squamous cell carcinoma (SCC). [6] Surgery can provide cure in localized cancers, whereas palliative chemotherapy or radiotherapy remain the mainstay of treatment in non-resectable and metastatic cancers. [7] These cancers can also present in combination with urothelial cancers as mixed histologies. All mixed or pure NUBCs are considered high-risk disease and generally have a poor prognosis as compare to patients with TCCs, and patients usually present at an advanced stage. [8]

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. [9]

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. [10] Transuretheral 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. [11]

The objective of the present study was to oncologic outcomes in patients with nonurothelial bladder cancer in Bihar region.

Materials and Methods

The present study was conducted in the Department of medical oncology, IGIMS, Patna, Bihar, India for one year. The patients diagnose with bladder cancer and refereed to our hospital were enrolled in the present study.

Inclusion & 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.

Methodology

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 was 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.

Results

Table 1: Variables

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

Majority of the cases were Urothelial cell carcinoma (50%) followed by Squamous cell carcinoma (16.66%). Most of the patients in the study were married male. The maximum number of patients fell under T1 stage and N0 stage.

Table 2: Three years overall and disease‑specific survival (with 95% confidence intervals) and unadjusted hazard ratios by histology

Histology	3 years OS	HR OS	P	3-years DSS	HR DSS	P	Median OS (years)	Median DSS
UCC	55.4% (54.5-56.4)	1 (referent)	-	63.7% (62.9–64.8)	1 (referent)	-	4.0	11.3
SCC	44.8% (40.8–48.8)	1.35 (1.23–1.50)	<0.001	52.3% (48.0–56.4)	1.46 (1.29–1.64)	<0.001	2.3	3.8
AC	58.7% (52.8–64.1)	0.93 (0.79–1.08)	0.3	65.3% (59.3–70.6)	0.95 (0.79–1.14)	0.6	4.5	10.8
Sarcoma	37.4% (28.2–46.5)	1.74 (1.39–2.17)	<0.001	45.4% (35.1–55.1)	1.91 (1.49–2.47)	<0.001	1.4	2.2

Small cell	37.2% (27.7–46.8)	1.59 (1.26–2.00)	<0.001	41.6% (31.3–51.6)	1.91 (1.48–2.46)	<0.001	1.4	1.9
Signet ring	35.9% (24.8–47.2)	1.43 (1.08–1.89)	0.010	44.2% (31.6–56.2)	1.64 (1.21–2.24)	0.001	2.0	2.3
Spindle cell	44.8% (34.2–54.8)	1.41 (1.09–1.82)	0.009	52.6% (41.5–62.6)	1.57 (1.17–2.09)	0.002	2.0	4.3

The univariable hazard ratio (HR) and 3‑year and median OS and DSS by histologic subtype. With the exception of AC, all nonurothelial bladder cancers have a worse 3‑year OS and DSS when compared to UCC. The worst DSS was demonstrated in small cell histology with 3‑year survival probabilities of 41.6%.

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. [12-14] 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. [12]

T1 carcinoma of the urinary bladder is a heterogeneous disease with potentially aggressive behavior leading to lethality. [15] 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. [16] 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. [17] 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. [18,19]

While UCC is the most common histology for patients undergoing radical cystectomy, histologic variants comprise a substantial number of patients undergoing radical cystectomy in the United States. Using a large administrative data set, we report an incidence of nonurothelial cancer of approximately 10% in patients undergoing radical surgery. This is high relative to previous studies which report rates ranging from 5% to 10%. [1,2] AC had similar OS and DSS to UCC. Ploeg et al. demonstrated a similar finding in an analysis of the nationwide Netherlands Cancer Registry in all patients with >T1 disease where patients with urothelial carcinoma and AC had similar relative 3‑year survival rates of 37% and 39%, respectively. [20]

Small cell carcinoma of the bladder also had similar overall and DSS compared to urothelial carcinoma on multivariable analysis despite having worse 3‐year survival on log‐rank test. This finding may be secondary to the small number of patients with small cell carcinoma in our data set. A recent case–control study matched 68 patients with small cell carcinoma of the bladder with 138 patients with urothelial carcinoma of the bladder with similar TNM stage who received radical cystectomy. [21] Besides AC and small cell carcinoma, the remaining analyzed 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. Finally, discordancy between transurethral resection of bladder tumor (TURBT) specimens diagnosed at pure urothelial carcinoma and final radical cystectomy histologic designation of mixed histology may preclude certain patients from receiving potential neoadjuvant multimodal therapy.

Differences in survival may be related to lower utilization of chemotherapy for variant histologies, for which there is no consensus regimen. The role of neoadjuvant and adjuvant chemotherapy in patients with variant histology has received some recent attention but remains poorly understood. In a secondary analysis of the SWOG 8710 study which evaluated survival in patients with stage T2‐T4a bladder urothelial carcinoma undergoing cystectomy versus cystectomy plus neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy, there was a survival benefit in the patients with mixed histology (urothelial carcinoma + squamous and glandular differentiation) (HR 0.46; 95% CI: 0.25–0.87; P = 0.02). [22]

Furthermore, there was no central pathology review, which may have resulted in misclassification of these rare and often difficult to characterize bladder histologies. Finally, it is impossible to determine whether histologic variant occurred in the presence of absence of coexisting UCC. [23]

Conclusions

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. In particular, sarcoma, spindle cell, and signet ring variants were particularly aggressive malignancies, more so even than small cell carcinoma of the bladder. Further research is needed to better understand the unique biology of these nonurothelial bladder cancer histologies as well as the optimal timing and modes of therapy to improve the long‐term outcomes in affected patients.

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