

## Genitourinary/Gynecologic Cancer

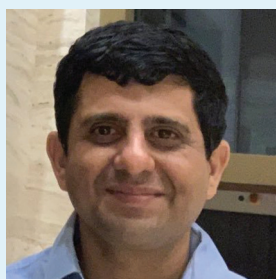
# Nonbilharzial Squamous Cell Bladder Cancer: An Indian Experience

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## Abstract



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### Keywords

- ▶ bladder cancer
- ▶ cystectomy
- ▶ carcinoma, squamous cell
- ▶ non-Bilharzial

**Background** Squamous cell carcinoma represents the second most common histological type of bladder cancer. Nonbilharzial squamous cell carcinomas of bladder are rare histological variant with limited experience.

**Objective** We aimed to review our experience to determine various treatment patterns and survival outcomes for this malignancy.

**Methods** Data from patients treated at our center from 1995 to 2016 was collected from patient records and analyzed. Clinicopathological variables, treatment patterns, and follow-up data were extracted.

**Results** A total of 32 patients were included in the study with a median age of 55.5 years. Hematuria was the most common presentation. Overall, 16 patients underwent radical cystectomy, 8 underwent definitive radiotherapy (RT), 4 received palliative RT, and 4 patients defaulted for any treatment. Surgery conferred better survival rates as compared with RT (31.9 vs. 7.45 months). In the surgical group, only pathological TNM staging was a significant prognostic factor.

**Conclusion** In localized nonbilharzial squamous cell bladder cancer, radical cystectomy with bilateral pelvic node dissection appears to be treatment modality of choice. Larger series are needed to validate the role of other perioperative modalities.

## Introduction

Bladder cancer is the commonest malignancy of the urinary system and ninth most common malignancy site wise. Squamous cell carcinoma (SCC) represents the second most common histological type of bladder cancer.<sup>1</sup> Epidemiologically, it has been divided into two categories: those associated with *Schistosoma hematobium* typically occurring in Egypt and Middle East and those arising de novo or nonbilharzial SCC.

Nonbilharzial SCC is a rare disease forming 2 to 5% of all bladder cancer patients.<sup>2</sup> Owing to its rarity, most data are derived from single-institution experiences leading to lacu-

nae in the management strategies. Also, there is a paucity of data from the Indian subcontinent. This series contributes by evaluating the clinicopathological characteristics and patient outcomes of SCC bladder treated at our institution.

## Materials and Methods

We performed a retrospective analysis on all patients with biopsy-proven SCC bladder who underwent treatment at our institute from 1995 to 2016. Patient characteristics including age, gender, previous smoking history, presenting complaint, Charlton comorbidity score, and history of previous bladder

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surgery were collected. Treatment patterns and follow-up data were gathered from electronic records.

All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., IBM, Chicago, Illinois, United States). Student's *t*-test was used for nonparametric variables and the chi-squared test was used for categorical variables with the level of significance set at  $p < 0.05$ . OS (overall survival) was calculated from date of diagnosis to date of death due to any cause. Survival curves were generated using the Kaplan–Meier method and compared using the log rank test.

## Results

A total 2,088 patients were diagnosed with bladder cancer in the above-mentioned research period, of which 32 were SCC histology (1.53%). The median follow-up duration was 66 months (0.9–124.1). The clinicopathological profile of the is presented in **Table 1**. Males were affected 1.6 times more than females with hematuria being the most common complaint. However, in contrast to males, majority of females presented with palpable growth (58.3% male, 5% females;  $p = 0.001$ ), performance status 2 (41.7% male, 15% females;  $p = 0.092$ ), and hydroureteronephrosis (HUN) (58.3% male, 25% females;  $p = 0.059$ ). Three patients had a history of previous surgery including suprapubic cystostomy, diverticulectomy, and cystolithotomy, whereas two had patients had a history of prolonged urinary catheterization for lower urinary tract symptoms.

The treatment details of the patients are presented in **Table 2**. Of the 30 patients with nonmetastatic disease, only 16 underwent radical cystectomy with bilateral pelvic nodal dissection. Eight patients received definitive radiotherapy (RT), four had locally advanced disease, three did not consent for surgery, and one patient had poor performance status. Four patients defaulted and did not receive any treatment. Two metastatic and two nonmetastatic patients received hemostatic RT for excessive bleeding.

In the 16 patients who underwent radical surgery, all had muscle invasive disease. **Table 3** gives the clinicopathologic features of surgical patients. Nodal involvement was seen in four patients, two had obturator nodes, one had bilateral iliac, and one had perivesical node. Frequency of nodal metastasis for pT2, pT3, and pT4a was 0, 28.6, and 100%, respectively. This suggested a significant relationship between pathological T and N stage ( $p = 0.005$ ). Three patients received adjuvant treatment in the form of weekly cisplatin with RT (dose 45–60Gy) for nodal involvement and margin positivity. Two patients with node positive disease were unfit for adjuvant treatment.

On follow-up, of the 8 patients who received definitive RT, four had residual disease at the end of treatment, one developed distant metastasis, and only one was disease free. Data was not available for two patients. The 5-year OS for the entire cohort was 32.4%. On survival analysis, surgery conferred the best survival followed by radiation and dismal for palliative RT/or defaulted group ( $p < 0.05$ ). The median survival for patients treated with surgery and RT was 31.9

**Table 1** Clinicopathological characteristics of the patients

Characteristic	Number of patients
Median age [years] (range)	55.5 years (30–78)
Gender	
Male	20 (62.5%)
Female	12 (37.5%)
History of tobacco usage	
Present	18 (56.3%)
Absent	14 (43.8%)
History of previous bladder surgery or prolonged catheterization	5 (15.6%)
Symptoms	
Hematuria	18 (56.3%)
Pain	6 (18.8%)
Lower urinary tract symptoms	8 (25%)
Charlton comorbidity score	
0	24 (75%)
> 1	8 (25%)
Palpable growth at presentation	
Absent	24 (75%)
Present	8 (25%)
Urine cytology	
Positive	9 (28.1%)
Negative	5 (15.6%)
Inconclusive	9 (28.1%)
Not available	9 (28.1%)
Grade	
I	1 (3.1%)
II	10 (31.3%)
III	21 (65.6%)
Hydroureteronephrosis	
Absent	20 (62.5%)
Present	12 (37.5%)
Nodal involvement	
Absent	24 (75%)
Present	8 (25%)
Distant metastasis	
Absent	30 (93.8%)
Present	2 (6.3%)

and 7.45 months, respectively. The 2-year disease-free survival for the patients who underwent surgery was 71.1%. Except pathological TNM stage, no other variables (age, gender, Eastern Cooperative Oncology Group performance status, tumor grade, HUN, addiction, adjuvant treatment) had significant impact on OS for patient who underwent

**Table 2** Treatment modalities and their median OS

Treatment modality	Number of patients	Median OS in months (range)
Surgery	16	31.9 (3.3–124.1)
II	7 (43.8%)	62.6 (3.3–124.1)
IIIA	7 (43.8%)	30.9 (3.7–109.7)
IIIB	2 (12.5%)	11.7 (8.4–15.0)
Radiation	8	7.45 (1.7–42.7)
Palliative RT	4	6.1 (4.7–7.2)
Defaulted	4	1.1 (0.9–7.6)
All patients	32	8.4 (0.9–124.1)

Abbreviations: OS, overall survival; RT, radiotherapy.

surgery. Three patients recurred on follow-up with two having distant metastasis (bone, lung) and one having local recurrence.

## Discussion

Non bilharzial SCC is a rare histological variant that accounts for less than 5% of all bladder cancers.<sup>3</sup> At present, there is very limited resource to guide clinicians regarding the treatment options for this morbid malignancy. To our knowledge, this is the largest series of cases reported from Indian subcontinent. It has typically been reported to be a disease of advanced age; however, the median age of our cohort is nearly 10 years younger.<sup>3</sup> The demographic pattern is similar to that reported in the Western literature with males being afflicted 1.6 times more than females and females presenting with advanced disease at presentation.<sup>4</sup> Various factors like smoking, chronic indwelling catheter, chronic urinary tract infection, bladder diverticulum, and vesical calculus have been implicated in the etiopathogenesis of bladder SCC.<sup>5</sup> In our series, more than 50% patients had a history of smoking; however, no significant association was noted. Hematuria was the most common presenting symptom. SCC bladder tends to present at advanced stage as compared with their urothelial counterparts.<sup>3</sup> Nearly one-fourth of patients had palpable growth at presentation and HUN was noted in 37% of the patients, which are usually signs of advanced disease.

Urine cytology is very specific for detecting high-grade urothelial carcinoma. In one review, the authors found that only 25% of the patients having atypical squamous cells in urine had squamous cell bladder cancer and it most commonly represented vaginal contamination in females and distal urethral exfoliation in males.<sup>6</sup> In our study, only one-fourth patients had a positive urinary cytology, thereby limiting its clinical utility as a screening tool.

The paucity of literature has led to various treatment modalities being tried for SCC bladder. Historically, RT was tried by Rundle et al in 52 patients with a very dismal 5-year survival rate of 1.9%.<sup>7</sup> In our series also, no patient receiving RT survived till 5 years. Although the patients selected for

**Table 3** Characteristics of patient who underwent surgery

Characteristic	Number of patients
Mean nodal yield (range)	25 (10–36)
Reconstruction	
Ileal conduit	15
Neobladder	1
Microscopic margin	
Negative	15
Positive	1
pT stage	
T1	0
T2	7 (43.8%)
T3	7 (43.8%)
T4a	2 (12.5%)
pN stage	
N0	12 (75%)
N1	2 (12.5%)
N2	1 (6.3%)
N3	1 (6.3%)
Adjuvant RT	3

Abbreviation: RT, radiotherapy.

definitive RT were advanced disease, presence of residual disease in 50% suggested poor response to the treatment.

More recent series from various institutions have recommended radical surgery as the treatment modality of choice. Histological studies have shown a 24% incidence of lymph node metastasis emphasizing upon the role of pelvic lymphadenectomy.<sup>8</sup> Kassouf et al reported their experience of 27 patients of which 20 underwent radical cystectomy. The 2-year OS of the patients who underwent radical cystectomy was 66.1% as compared with 47.6% of the entire group. In their multivariate analysis, only treatment by radical cystectomy and history of previous superficial transitional cell carcinoma transformed into SCC.<sup>9</sup> A similar improvement in survival was reported by Zahoor et al who concluded that hydronephrosis, age > 70 years, lymphovascular invasion, advanced T stage, and nodal metastasis were associated with poor prognosis.<sup>10</sup> When compared with urothelial histology, it is ambiguous whether SCC has similar or poorer prognosis.<sup>11</sup> In our study, the survival is similar to that of contemporary series; however, except for pathological T and N stage, no other factor influenced prognosis. Recently, nomograms based on multiple clinicopathological and therapy factors have been created from the surveillance, epidemiology, and end results database to predict survival; however, they still need to be validated on prospective models.<sup>12</sup>

The role of multimodality treatment has been evaluated by various investigators, though only sporadic reports have shown benefit. Many authors previously showed a survival benefit of preoperative RT followed by radical cystectomy.

Rausch et al reviewed the role of neoadjuvant and adjuvant strategies and recommended that preoperative RT should be considered only if patient cannot undergo surgery. On evaluating multiple series, the 5-year OS ranged from 22 to 50% using various multimodality strategies.<sup>13</sup> Although above being said, local recurrences are far more common than distant metastasis and thus any local consolidation therapy may prove beneficial in improving survival. We recommended adjuvant RT to all node positive and margin positive for SCC histology based on the results from Egyptian bilharzial bladder cancer studies.<sup>14</sup> There was no benefit seen in our patients, but this could be due to limited sample size. The role of neoadjuvant chemotherapy, which has shown benefit in urothelial carcinoma, is unclear at present for squamous histology, as no regimen has shown consistently sustained response.<sup>15</sup>

The limitations of this study include its retrospective nature, limited sample size, and incomplete follow-up data. Although there was no central pathology review, all histological diagnosis were made by experienced pathologist. As there are no definite guidelines for SCC bladder, various treatment modalities have been used. Ours is a single-institution experience restricting its applicability. The rarity of the disease will constrain conducting prospective trials and reliable recommendations may come from multi-institutional studies or registries only.

## Conclusion

Nonbilharzial SCC bladder is a rare disease usually presenting in advanced stage. Radical cystectomy with pelvic node dissection currently appears to be the treatment modality of choice. The role of perioperative treatment requires further validation.

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### Note

The study design complies with the Declaration of Helsinki ethical standards.

### Disclosure

The authors have nothing to disclose.

All authors have contributed equally in conception, performance of work, interpretation of data, and writing the article.

### Conflict of Interest

None declared.

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