

# Primary Carcinoma of the Female Urethra: Single Center Experience of 18 Cases

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**Background:** Primary carcinoma of the urethra is more common in women than in men. Vague symptoms in the early stages delay the diagnosis in most patients. Surgery and radiotherapy are used as treatment modalities for these tumors, either alone or in combination.

**Methods:** We retrospectively analyzed the records of 18 female patients with urethral cancer presented to our institution. Secondary tumors involving the urethra from adjacent organs like bladder carcinoma and gynecological cancer were excluded.

**Results:** In our review, the overall survival was 74% at 3 years and 33% at 5 years with median overall survival of 51 months. There was a statistically better overall survival in patients with early stage tumors compared with later stage disease ( $P = 0.03$ ) and patients with distally located tumors had better survival compared with proximal and whole urethral involvement.

**Conclusions:** The prognosis is poor in advanced stages and in those with proximal or whole urethral involvement, requiring extensive surgical procedures. The aim of treatment in distal urethral carcinomas should be local excision and radiotherapy, thereby preserving the bladder.

*Key words: carcinoma – radiotherapy – surgery – urethra*

## INTRODUCTION

Primary tumors of the female urethra are exceedingly rare and account for <0.02% of the malignant disease occurring in women (1). This disease usually presents late and, hence, has a poor outcome. Unlike bladder cancer, urethral carcinoma shows clinical and histological dissimilarities between male and female patients (2,3). Clinical management varies depending on the clinical stage and location of the lesion. There are no prospective randomized studies on which to base treatment of this disease. Surgery and radiotherapy have been advocated as effective treatment for early urethral cancers. Tumors arising from the distal urethra tend to be early stage and cure rates are high (4). However, due to rarity of this disease, there is no definite consensus regarding the treatment of choice for various stages. The 5-year disease-free survival is only 20–30% with surgical therapy only (5).

## PATIENTS AND METHODS

Tata Memorial Hospital is a tertiary cancer center in India and we manage about 170 cases of prostate carcinoma, 160 cases

of testicular tumors, 110 cases of penile cancer, 280 cases of bladder cancer and 150 cases of renal cell carcinoma per year. Total numbers of urethral cancers seen during 1991–2000 were 54, 36 male cases and 18 female. We analyzed the records of the 18 female patients with urethral cancer separately. Secondary tumors involving the urethra from adjacent organs like bladder carcinoma and gynecological cancer were excluded. The commonest presenting complaints were urethral bleeding or gross hematuria in 10 patients (55%), dysuria in eight (44%), urinary obstruction in seven (39%) and local mass in six (33%) patients. Two patients also had a history of pervaginal bleeding. Out of 18 patients, five had a history of repeated dilation of the urethra for stricture or persistent lower urinary tract symptoms and another two patients had repeated urinary tract infections. Five patients had a history of tobacco chewing. Mean duration of symptoms was 5 months.

Age of the patients ranged from 45 to 72 years with a mean of 58 years. Histopathological diagnosis was established in all cases, either by punch biopsy, transurethral resection biopsy or local excision of the tumor. Nine patients (50%) had squamous cell carcinoma, transitional cell carcinoma was seen in five patients (28%) and four patients (22%) had adenocarcinoma. All patients were evaluated by history and physical examination, blood chemistry, urinalysis, computed tomography (CT) scan, urethrocytostcopy, biopsy, examination under anesthesia and chest X-ray. Patients were staged according to AJCC-TNM classification. There were nine patients in stage I and

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stage II combined, five patients in stage III and four patients in stage IV. Nine patients had distal urethral involvement, five patients had entire urethral involvement and four had proximal urethral involvement. Groin nodes were positive in two patients, one unilateral and the other bilateral. None of the patients had distant metastasis at presentation. The modalities of treatment were surgery, radiotherapy or chemotherapy. Surgery was either local excision or anterior exenteration (cystectomy, hysterectomy, bilateral pelvic lymphadenectomy with ileal conduit). All patients were followed after completing the primary treatment. Patient survival was calculated by the Kaplan–Meier method and univariate analysis was done by using log-rank test for prognostic factor analysis.

## RESULTS

The treatment was based on extent of the disease, location of the tumor and general condition of the patients. The type of treatment received was: local excision with radiotherapy in two, anterior exenteration alone in four, anterior exenteration and adjuvant radiotherapy in four, radiotherapy alone in four, palliative radiotherapy in two patients and symptomatic treatment in two patients was the line of management. Out of nine patients with stage I and II combined, two who had a 2–3 cm lesion in the distal urethra were treated by local excision and local radiotherapy. Five patients underwent anterior exenteration and two patients in this group had received adjuvant radiotherapy. Two patients who had groin nodal disease, one unilateral and the other bilateral, underwent groin node dissection. Two patients received radiotherapy alone. Radiotherapy fields ensured the coverage of the primary tumor with margins and all the draining lymph including internal and external iliac lymph nodes, the lower common iliac lymph nodes and the medial inguinal lymph nodes. The doses delivered to the whole pelvis were in the range of 4500–5000 cGy, 180–200 cGy/fraction, five fractions/week for 4–5 weeks. The radiation dose of the primary was further escalated to a dose of 2000–2500 cGy so that the total dose delivered to the gross disease was in the range of 6500–7000 cGy. This boost was delivered by either further external radiation or by brachytherapy. There were mild complications (20%) from radiotherapy such as frequency of urination, dysuria, transient diarrhea and post-operative radiation fibrosis.

Follow up of the patients with stage I and stage II varied between 18 and 70 months. Two patients in this group, one who had local excision and radiotherapy, and another who had undergone radical cystectomy and radiotherapy, were alive at the end of 5 years. Six patients developed metastasis during follow up, with disease-free interval of 39 months.

Out of five patients with stage III, three underwent radical cystectomy and pelvic lymphadenectomy and ileal conduit with adjuvant radiotherapy and two received radiotherapy alone. Two patients received adjuvant chemotherapy with 5-fluorouracil and cisplatin. Two out of four patients in stage IV received only palliative treatment due to poor general condition and the other two had radiotherapy. Two of these

patients survived for 3 years, none survived for 5 years. All patients relapsed either loco-regionally or at distant sites, two patients received palliative chemotherapy and the others only symptomatic treatment.

The overall survival was 74% at 3 years and 33% at 5 years with median overall survival of 51 months. The disease-free survival was 36% at 3 years with a median disease-free survival of 26 months. A univariate analysis was done based on staging of the disease and location of the tumor. The median overall survival in patients with stages I and II combined was 60 months and overall 5-year survival was 50%. Patients with advanced disease in stages III and IV combined had a median overall survival of 43 months, 3-year overall survival of 56% and no 5-year survival with a statistically significant difference between the two groups ( $P = 0.03$ ) (Fig. 1). The median disease-free survival in these two groups was 51 and 23 months, respectively, with a significant difference ( $P = 0.04$ ) (Fig. 2).

Out of nine patients with proximal or whole urethral involvement, four received radiotherapy followed by surgery, two were unfit for any type of treatment and another two patients underwent radical surgery alone.

Patients with proximal and whole urethral involvement combined had a median overall survival of 31 months (5-year survival of 16%) and disease-free survival of 22 months, whereas those who had distal urethral involvement had a median overall survival of 60 months (5-year survival of 45%) and disease-free survival of 49 months which was statistically significant ( $P = 0.04$ ).

Out of nine patients with stage I and II disease, six had distal urethral lesions and three had either proximal or whole urethral involvement. The survival of patients with stage I and II was similar to the patients who had distal urethral involvement. Six patients with stage III and IV had either proximal or whole urethral involvement and three had distal urethral involvement. The survival of patients with stage III and IV was similar to the patients with proximal or whole urethral involvement. These

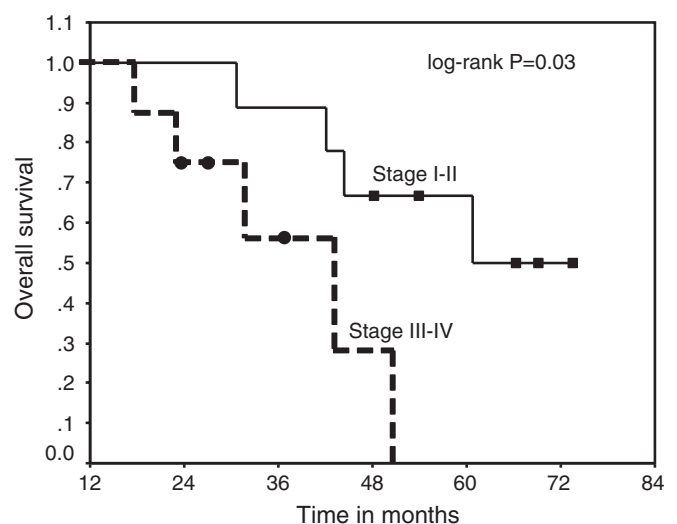
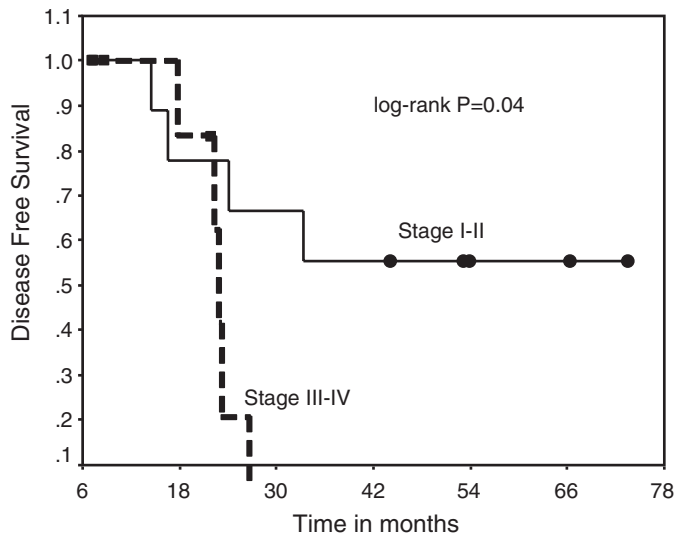


Figure 1. Overall survival according to stages I and II versus stages III and IV.



**Figure 2.** Disease-free survival according to stages I and II versus stages III and IV.

findings suggest that there is a correlation between the stage and location of the disease and overall survival.

However, there was no difference in the survival with regard to age, histological type, grade of the tumor, or presence of lymphadenopathy, although it is difficult to achieve statistical significance due to the small number of patients.

## DISCUSSION

Primary carcinoma of the female urethra is uncommon and no large scale experience with such cases has been published. Chu (6) reported that the incidence of disease varies from 1 in 1900 admissions at hospitals that exclusively serve indigent populations to 1 in 23 000 admissions at referral centers serving broader socioeconomic populations.

Various approaches in the management of patients with advanced urethral cancer have been employed. From the published literature, it appears that multimodality therapy may provide better disease-free survival rates; however, most of these reports are anecdotal (7–12). Combined radiotherapy and surgery has been suggested for entire urethral lesions and proximal urethral lesions (13,14). Tumors of distal urethra are amenable for local excision and organ preservation.

Garden et al. (15) reported a 5-year overall survival of 41%, Dalbagni et al. (16) a 32% overall survival and Foens et al. (17) a 33.5% survival. We had an overall 3-year survival of 74% and 5-year survival of 33% in our series of 18 patients.

Female urethral carcinoma appears to respond in early stages. Surgery, either local excision or radical surgery, is the treatment of choice for meatal or anterior urethral lesions (14). Our review supports the observation that the stage of the disease was the most important prognostic factor in the survival (18,19). In our series of patients, early-stage disease had 5-year overall survival of 50% and advanced disease had

3-year survival of 56% with no 5-year survival. The median disease-free survival in stages III and IV was 23 months, significantly ( $P = 0.04$ ) lower in comparison with stages I and II. Two out of four patients in stage IV received only palliative treatment due to poor general condition and the other two received palliative local radiotherapy.

Series in which patients are treated by irradiation alone report complication rates that range from 16 to 42% (18,20,21). A similar rate of complications (20%) was seen in our study.

Vague symptoms in early stage delay the diagnosis in most patients and tend to become refractory once the tumor grows to a large size. Bracken et al. (18) analyzed results with respect to tumor size and observed 5-year survival rates of 60, 46 and 13% for lesions that measured <2, 2–4 and >4 cm, respectively. As the exact size of the tumor was not recorded accurately at the initial evaluation of the patient, this parameter could not be analyzed in our series.

The relatively small number of patients with urethral cancer presented in our series limits statistical comparisons in treatment outcomes. However, there was a statistically better overall survival in patients with low stage tumors compared with higher stage disease ( $P = 0.03$ ) and, irrespective of therapeutic modality, advanced stage disease had a poor outcome. Our study supports the observation that a survival rate in patients with urethral cancer is related to the clinical stage of the disease and tumor location at the time of diagnosis (18,19). There is no valid consensus about the role of chemotherapy in female urethral cancer but systemic therapy may also improve the outcome of this tumor.

## CONCLUSIONS

Because of the rarity of this disease, there is no unanimous consensus regarding the treatment modality of choice for various stages. Half of our patients had locally advanced disease at the time of diagnosis and the outcome of treatment was poor. With a high index of suspicion, an attempt at early diagnosis should be made as low stage tumors have better overall and disease-free survival. Tumors located at the distal part of the urethra should be treated with either conservative surgery or radiotherapy or a combination of both with the aim of preserving the organ function, which has greater impact on quality of life.

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