Treatment and Outcomes of Primary Urethral Cancer

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Abstract

Objective: To evaluate the clinical data, pathological types, treatment methods, and long-term outcome of 17 cases on Primary Urethral Cancer (PUC).

Patients and Methods: We did a retrospective review of 17 patients diagnosed with PUC from January 2011 to December 2020 at four hospitals in Gansu Province. We stratified the patient concerning to their age, gender, histological type, stage, treatment modality and final follow-up, among which those at an early stage were defined as Tis-T2N0M0, while those at an advanced stage as T3-4. Then we analyzed the stratified samples based on clinical stage, treatment method, and outcome.

Results: The majority of the 17 patients were female (F: M=13:4), And the number of cases at an early stage is roughly the same as those at an advanced stage (9:8). The most common histologic types were squamous cell carcinoma (35.3%) and urothelial carcinoma (35.3%), while adenocarcinoma (11.8%), malignant melanoma (11.8%), and small cell carcinoma (6.9%) accounted for a relatively small proportion. Surgery was a primary treatment modality for early cases, While for advanced cases, multimodal treatment was preferred.

Conclusion: Survival rates are significantly lower in rare tumors than common tumors; besides, patients with early-stage PUC show better outcomes thanks to the single-mode therapy, whereas patients with advanced cancers need the most advanced multimode treatment to benefit patients as much as possible. However, due to the rarity of this malignancy, multi-agency experience provides the best evidence available.

Introduction

Primary urethral carcinoma(PUC) is a rare malignant tumor that accounts for < 1% of all malignant tumors worldwide[1]. In Europe, the estimated annual incidence of PUC is 650 new cases (age-standardized ratio, 1.6 / million for male and 0.6 / million for female)[2]. The figure is three times higher than that of the United States (4.3 / million men and 1.5 / million women)[3]. The incidence rate is almost three times higher in men than in women, and in the United States, the age of onset of PUC in both men and women is about 60 years and beyond⁴. The incidence rate of the elderly (> 75 years) is rising[1]. The etiology of PUC includes chronic urinary stimulation caused by catheterization, chronic inflammation secondary to infection, radiation, diverticulum, and stricture. The association between squamous cell carcinoma (SCC) and genital sclerosing moss also has been reported as a potential risk factor[1]. There are multiple histological subtypes of PUC, and different treatments need to be developed based on different cell sources, biology, and clinical behavior. The histologic types of PUC are classifying according to 2016 WHO typing: the predominant one is urethral carcinoma(UC,54–65%), followed by squamous cell carcinoma (SCC,16–22%) and adenocarcinoma (AC,10–16%), as well as some other less common histologic types including melanoma, small cell carcinoma, and sarcoma. The subtypes are unevenly distributed between the sexes and the differences in their origin can be explained by the different urethral

anatomy between the sexes[1, 5]. The pathological type of the tumor varies with onset position. Proximal PUC is usually a tumor characterized by urothelium. In contrast, distal PUC, especially those involving the urethral orifice, is usually of the squamous cell type and may be associated with the extension of primary male lesions in glans and prepuce or female primary lesions the vulva. The distal PUC of male samples is probably related to differentiated and undifferentiated penile intraepithelial neoplasia (PeIN). In addition, in the globular and membranous parts of the male urethra, there are basal-like features and both squamous and uroepithelial carcinomas, which occur in association with HPV infection clinically invasive, usually with local lymph node metastasis and distant organ metastasis[6].

Due to the rarity of PUC cases and their aggressive nature, very few studies are about PUC, mostly are case reports. Therefore, it is not easy to reach a consensus on the best treatment modality for PUC. Although surgery alone has been identified as an effective treatment for low-stage urothelial carcinoma, surgery alone, radiotherapy and chemotherapy can not provide good outcomes. To further study and summarize the clinicopathological features, treatment methods, and outcomes of PUC, we now summarize the characteristics of the 17 cases mentioned above.

Patients And Methods

We conducted a retrospective analysis of 17 patients with PUC at four hospitals in Gansu Province from January 2011 to December 2020. There were 10 cases in Lanzhou University Second Hospital, 4 cases in Gansu Provincial People's Hospital, 2 cases in Lanzhou University First Hospital, and 1 case in Chinese People's Liberation Army Joint Logistics Support Unit 940 Hospital. Then we added pathological stages and showed the histological type of these cases. Pathological staging relied on urethroscopy, tumor biopsy, cystoscopy, and pelvic CT. Early cases were Tis-T2N0M0, and advanced cases were T3-4, N+, or M+. One AC case was treated with docetaxel chemotherapy, and two UC were treated with pirarubicin chemotherapy.

The assessed variables included gender, clinical manifestation, histological type, stage, treatment, and survival time. Endpoints included cause-specific disease, death from other or uncertain causes, and no evidence of disease at the last follow-up. Survival time was defined as the time from diagnosis to the endpoint. Kaplan-Meier curves were constructed to assess overall survival for the entire study group and survival for common and rare tumors. Analyses were based on clinical staging, treatment, and outcome.

Results

Of the 17 patients, 4 (23.5%) were male and 13 (76.5%) were female, age (61.3 ± 12.0), average follow-up time was 49.5 months (range: 3–96 months), and histology types were as follows: UC in 6 cases (35.3%), SCC in 6 cases (35.3%), AC in 2 cases (11.8%), malignant melanoma in 2 cases (11.8%), and 1 case of small cell carcinoma (6.9%). The lesions were: 14 cases (82.4%) in the anterior urethra, 2 (11.8%) in the posterior urethra, 1 (6.9%) in the whole urethra. 9 cases (52.9%) in the low stage tumor group and 8 in the high stage tumor group (47.1%) (Table 1).

Table 1
Characteristics of the Participants

Gender	
Male	4 (23.5%)
Female	13 (76.5%)
Age/ yrs	61.3 ± 12.0
Tumor location	
anterior urethra	14 (82.4%)
posterior urethra	2 (11.8%)
whole urethra	1(6.9%)
Pathological diagnosis	
UC	6 (35.3%)
SCC	6 (35.3%)
AC	2 (11.8%)
Malignant melanoma	2 (11.8%)
Small cell carcinoma	1 (6.9%)
Stage	
Low	9 (52.9%)
High	8 (47.1%)

The 5-year overall survival rate was approximately 40% in 17 patients (Fig. 1). All patients with low-stage cancer underwent surgical treatment, and the most commonly used surgical method was local lesion resection. One patient underwent total urethrectomy + total cystectomy, and two of the 9 patients received chemotherapy. Three patients with SCC were lost during follow-up, and one patient with malignant melanoma died after 2 years of follow-up due to tumor progression. Partial urethrectomy, local lesion resection + chemotherapy, total urethrectomy + total cystectomy (female + uterus and bilateral appendages), and total urethrectomy + radiotherapy (Table 2). One patient with SCC was lost to follow-up, one patient with small cell carcinoma died of tumor progression after 2 months of follow-up, one patient with SCC died of renal failure after 3 years of remaining patients are still alive at follow-up. SCC was almost the same equally represented in the early and advanced cancer groups, while UC was more frequent in the early stage (Table 2). Long-term survival was significantly lower in the high-stage cancer group than in the low-stage cancer group.

Table 2
Treatment Outcomes With Urethral Cancers

Pathological diagnosis					
Patient Profile	SCC	UC	AC	Malignant melanoma	Small cell carcinoma
Number	6	6	2	2	1
Gender					
Male		3		1	
Female	6	3	2	1	1
Age, years	60.8 ± 2.5	61.5 ± 17.8	52.5 ± 3.5	66.0 ± 19.8	71.0 [#]
TNM					
T ₁ N ₀ M ₀	3	4	1	1	
T ₁ N ₂ M ₀			1		1
T ₃ N ₀ M ₀	3	1			
T ₃ N ₂ M ₁				1	
T ₄ N ₁ M ₀		1			
treatment method					
Partial urethrectomy	4	3		1	
Partial urethrectomy + CHT		2	1		
RCU	2	1	1	1	
RCU + RCT					1
CHT:chemotherapy;RCT:radiochemotherapy;RCU: radical cyst(oprostat)ectomy with total urethrectomy					

There were five pathological types in this group of patients. Uroepithelial carcinoma and squamous carcinoma accounted for most of them. UC microscopy showed papillary proliferation of cancerous tissues with extremely disorganized cell arrangement and varying size(HE ×40, Fig. 2A).

Immunohistochemical staining showed that CK20(-), P63(+), CK7(+), Uroplakin III(-), P53(+ 20%),AR(-), GATA3(-), Ki67(+)80%. SCC was seen microscopically as an infiltrative growth of heterogeneous cell nodules with eosinophilic cytoplasm, increased nucleoplasmic ratio, heterogeneous deep staining, and incomplete keratinized beads in the center of a few nodules(HE ×100,Figure 2B). Immunohistochemical staining showed that CK7-, CK20-, p16+++, GATA3-, Uroplakin⊖, PSA-, p63+++, p40+++, p53 < 10%+, AR-

Ki67(90%+). Malignant melanoma is seen microscopically as tumor cells of different sizes and morphologies, round, ovoid or polygonal, with eosinophilic cytoplasm, increased nucleoplasm ratio, obvious nucleoli, eosinophilic nuclei in some nuclei, nuclear schizophrasia, and epithelial phagocytosis in some areas(HE ×100, Fig. 2C). Immunohistochemical staining showed that HMB45(+++) MelanA(+++), Vimentin(+++), S-100(+), h-caldesmon(+), CD138(+), CD38(-), CKpan(-), CD30(-), CD20(-), CD3(-), Desmin(-), Ki67 proliferative active zone 40%+. Small cell carcinoma was seen microscopically with the diffuse distribution of small heterogeneous cells, slightly irregular nest-like and beam-like, with abnormal nuclei, fine chromatin, obvious nucleoli, many schizophrastic images, unclear cell boundaries, apoptosis, interstitial fibrous tissue hyperplasia, and abundant small blood vessels(HE ×200, Fig. 2D). Immunohistochemical staining showed that Syn(+), EMA(Partially +), CEA(-), CK7(Partially +), CK20(-), S-100(-), PGP9.5(+), P53(+), CD45(-), CD3(-), CD20(-), CgA(+), Ki-67(index:>90%). AC was seen microscopically with the glandular duct-like arrangement of heterogeneous cells, cancerous tissue infiltrating the interstitium, mucus secretion by cancer cells, and mucus lake formation(HE×100, Fig. 2E). Immunohistochemical staining showed that CK7(-), CK20(+), CEA(+), CKH(+), CKL(+), P53(-), Ki-67(40%), Villin(+).

Discussion

Independent prognostic factors affecting the survival of patients with PUC are the age of onset, race, histological type, AJCC stage, and surgical status, and older patients and blacks usually have a poorer prognosis. The 5-year and 10-year survival rates of PUC patients were 46% and 31% respectively[6, 7, 8, 9]. A recent study analyzed the pathological types of PUC and found that survival rates were lower in the rare pathology group than in the joint pathology group (UC, SCC, AC)[5]. In our study, it was also confirmed that the overall prognosis of rare tumors is lacking(Fig. 3). Compared with men, the survival of women with AC was worse. Compared with AC or SCC, the survival of male patients with UC is worse[8, 10]. Some scholars believe that the prognosis of distal urethral lesions is worse than that of penile tumors¹ and better than that of prostatic urethral tumors. However, other scholars believe that the prognosis of a distal urethral tumor is better than that of a proximal urethral tumor[11, 12].

Approximately 50% of patients have locally advanced disease by the time they become symptomatic, and the tumor has the characteristics of solid invasion and rapid progress, which makes the treatment more difficult. In localized PUC, penis preservation is feasible for men, while complete urethrectomy is recommended for women to minimize the recurrence caused by a positive margin. Multimodal therapy significantly improves the local recurrence rate and overall survival rate of proximal PUC. For these reasons, multimodal therapy has become the standard gold treatment for proximal PUC[1]. The local advanced PUC should be treated with multi-mode, and the scope of operation is more likely to be radical prostatectomy and total urethrectomy (RCU). Combined radiotherapy and chemotherapy (CHT) can improve survival rate, and the new platinum drug CHT can improve the prognosis of patients[1, 3]. Cahn et al. Also confirmed that the use of multimodal therapy (surgical resection + systemic therapy + radiotherapy) has a survival benefit for PUC with UC; however, in their study, no survival benefit has been

confirmed for SCC or AC[9]. It is not yet clear whether multimodal therapy is beneficial for other rare pathological types, and more clinical studies are needed to confirm⁵. However, Gakis et al. found that patients with recurrent PUC who received salvage therapy had better survival than patients who did not[13]. Perioperative chemotherapy[14] and post-chemotherapy consolidation surgery[15] in the local patients in the late stage of long-term survival. Therefore, the optimization of the treatment of advanced urethral cancer has become the focus of international medical and health institutions, aiming to improve the oncology efficacy and quality of life of patients with rare malignant diseases.

The disadvantage of this study is that the loss of follow-up rate (23.5%) is too high to compare survival differences. In addition, like most PUC case studies, the number of patients in this study is small and therefore may not be representative of the general population. In epidemiology, PUC is dominated by UC, but the number of SCC and UC in this sample is the same. The sample size of this study is not large enough to provide statistical significance for all the exploration results. More prospective clinical studies with reliable evidence are needed for better treatment of the disease.

Conclusions

In summary, Our study confirms that Survival rates in PUC are significantly lower in rare tumors than common tumors. Early tumors have a good prognosis, while advanced tumors should be treated with multimodal therapy. Due to the rarity of the tumor, further observation is needed with the support of multi center and multi sample.

Declarations

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Availability of data and materials

Raw data may be requested from the authors with the permission of the institution.

Ethics approval and consent to participate

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study received the Lanzhou University Second Hospital Ethical Committee approval (2017A-053).

Authors' contributions

Shujun Yang and Shun Wang have performed data statistics and paper writing. Gui Ma analyzed the pathological results, Duo zheng, Yongsheng Ying and Weiping Li provided some clinical data. Panfeng Shang proofread the article.

Consent for publication

Not applicable

Competing interests

All authors have no conflicts of interest or financial ties to disclose.

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Figures

Figure 1

Figure 2

(A) UC showed papillary hyperplasia, disordered cell arrangement, and varying size (HE×40). (B) SCC showed infiltrative heterotypic cell nests with eosinophilic cytoplasm, and a few of them had incomplete keratinizing beads in the center (HE×100). (C) Malignant melanoma has different size and different shape under the microscope, and phagocyte is seen in some areas (HE×100). (D) small cell carcinoma showed diffuse distribution of heteromorphic small cells (HE×200). (E) adenocarcinoma showed a tubular arrangement of heteromorphic cells, and the formation of mucus lake could be seen (HE×100).

Figure 3

Overall survival in common cancers and rare cancers