Introduction

Transitional cell carcinoma of urinary bladder (TCCB) in childhood is rare, with only some 100 cases occurring in the first 2 decades of life. The related literature is limited. Therefore, the clinicopathological features, appropriate treatments and prognostic outcomes remain unclear. We retrospectively reviewed 4 consecutive patients (4 males, 0 female; age ≤ 18 years) who were diagnosed with TCCB and treated in our hospital between 1980 and 2013. The clinicopathological features, treatment strategies and prognostic outcomes were reviewed from the medical records. To our knowledge, no such studies from China have been reported in English.

Case Reports

The clinicopathological characteristics are described in Table 1.

Case 1
An 11-year-old male, presented with dysuria and abdominal pain for one year. Urinary tract ultrasound revealed a 1.6 × 1.1 cm solid lesion. Cystoscopy confirmed that the location was in trigone area of the bladder. Due to the risk of urethral damage, we used ureteroscopy (F8/9.8 wolf, made in Germany) with holmium laser, which has a relatively smaller caliber to excise the lesion. No postoperative intravesical instillation therapy was administered. Histological exam showed low-grade papillary urothelial carcinoma (LGUC) without invasion. Urinalysis and ultrasound were performed once every six months in the second year. Thereafter, urinalysis and ultrasound were performed once a year, whereas cystoscopy was considered only when abnormalities were detected via ultrasound. During the follow-up period (50 months), no relapse was observed.

Case 2
A 15-year-old male, presented with painless gross hematuria for 5 months. Preoperative urinary ultrasound detected a papillary lesion (0.7 cm in diameter) located at the bladder neck. The lesion was then excised endoscopically. Histological analysis showed LGUC with lamina propria invasion (pT1). The patient did not have postoperative intravesical instillation therapy. Following the same surveillance regime as case 1, no recurrence was observed during follow-up (86 months).

Case 3
A 17-year-old male, presented with terminal painless hematuria without other associated symptoms. A 1.6 × 0.9 cm papillary lesion was detected and confirmed via ultrasound and subsequent cystoscopy. Then, transurethral resection was carried out. Postoperative pathological analysis revealed LGUC without evidence of invasion (pTa). As the patient was involved in a clinical trial of hydroxycamptothecin (HCPT), a multiple intravesical instillation of HCPT was administered postoperatively. With the same surveillance regime, no recurrence was observed during follow-up (24 months).
was also demonstrated by Javadpour and colleagues. On the other hand, no patients in our series, had associated cigarette smoking.

Table 1. The clinicopathological characteristics of 4 pediatric TCCB patients.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Cigarette smoking</th>
<th>Family history</th>
<th>Presenting symptom</th>
<th>Grade</th>
<th>Stage</th>
<th>Intravesical therapy</th>
<th>Follow-up (months)</th>
<th>Recurrence</th>
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<td>T1</td>
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<tr>
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<td>LGUC</td>
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</tr>
</tbody>
</table>

LGUC = low-grade urothelial carcinoma; HCPT = hydroxycamptothecine; TCCB = transitional cell carcinoma of bladder

Table 1. The clinicopathological characteristics of 4 pediatric TCCB patients.

Case 4
A 14-year-old male, presented with intermittent gross hematuria for 1 month. The ultrasound showed a 3.9 × 2.0 × 2.4 cm papillary lesion with a confirmed location at the trigone area of bladder (by subsequent cystoscopy). It was excised endoscopically without postoperative instillation chemotherapy. The histological examination revealed LGUC without evidence of invasion. Using the same surveillance regime, no evidence of recurrence was observed during the follow-up period (28 months).

Discussion
The peak incidence of TCCB occurs in the sixth decade. However, TCCB in young patients is rare, less than 1% of such cases occurring in the first 3 decades of life. Furthermore, Javadpour and colleagues found that only 38 out of 10,000 patients who presented with TCCB were under the age of 20. To our knowledge, there are some 100 reported cases of TCCB under the age of 20, among which only 20 are below 10 years of age. Men are three to four times more likely to develop bladder cancer than women. In the adult population, several risk factors have been well defined, especially the history of cigarette smoking, by which the gender-specific difference in the incidence can be well explained. However, it is worth noting that the male predilection is also maintained in the young population. Previous studies had reported a male-to-female ratio of 3:1 to 4.75:1. Benson and colleagues reported a series of pediatric TCCB patients, among which six (50%) were smokers. A similar smoking history rate (47.4%) was also demonstrated by Javadpour and colleagues. On the other hand, no patients in our series, had associated cigarette smoking history, which was consistent with a few other studies where a low likelihood of smoking history in this age population was reported. Thus, the association of cigarette smoking with the development of TCCB in the pediatric population is somewhat questionable. In addition, comparative studies have demonstrated that those pathogenetic mechanisms contributing to the formation of TCCB in the elderly are not detected in the young population, especially those under 20 years, suggesting alternate mechanisms of tumorigenesis.

Similar to previous studies, the major initial presenting symptom was gross hematuria. However, owing to the rarity of these tumors in the pediatric population, a diagnosis of TCCB is difficult to be associated with hematuria. In our series, the interval between the onset of symptoms and the final diagnosis of TCCB ranged from one month to one year. Therefore, we suggest that the possibility of TCCB in children with hematuria should be borne in mind. Ultrasound was reported as an effective tool in detecting intravesical lesions, with a sensitivity ranging from 85% to 100%. Similarly, intravesical lesions were detected using bladder ultrasound in all our 4 patients. Furthermore, combined with the ultrasound, which is of non-invasive nature, we recommend renal and bladder ultrasound to be the most appropriate initial diagnostic means for young patients suffering from hematuria to rule out the presence of TCCB.

Most series have reported that TCCB in childhood is of low-grade and excellent prognosis compared with those of older patients. Histological analysis of our study revealed 4 cases of LGUC, all of whom were non-muscle invasive lesions (only 1 invaded the lamina propria). Owing to the non-invasive biological behavior, transurethral resection was performed in all patients and considered as the general principle of therapy for children. In adults, postoperative intravesical instillation therapy should be performed among non-muscle invasive cases regularly. However, the indolent biologic behavior of these tumors in the pediatric population complicates matters. In a recent large series, none of the 23 patients underwent postoperative instillation therapy, except one non-invasive LGUC who received mitomycin at the time of transurethral resection. Such cases are also limited in the literature. In our series, all the patients underwent transurethral resection alone, but one underwent postoperative multiple intravesical instillation of HCPT. No evidence of tumor relapse or progression was observed during follow-up. On the other hand, Khandelwal and colleagues first reported a 5-year-old boy, presenting with high-grade TCCB, who was successfully treated with partial cystectomy and intravesical Bacille Calmette-Guérin (BCG). They asserted postoperative intravesical therapies were essential for high-grade TCCB patients to prevent the recurrence or progression of the tumor, since this tumor is more likely to recur or progress than low-grade cases. Considering the rarity of these tumors and the lacking knowledge of mechanisms of tumorigenesis in the pediatric population, it is unlikely to well establish the standard of adjuvant medical therapy for patients with TCCB in this age. Thus, there is an urgent need to identify factors affecting the prognosis of TCCB in the young population, which will allow a guideline in this field to be established. However, according to the mentioned study, postoperative instillation therapy seems to be an appropriate adjuvant medical therapy for high-grade TCCB patients, because of the possibly higher risk of recurrence and progression.

Performing a cystoscopy or a transurethral resection for a male patient at such a young age remains a challenge for urologists, due to the immature urethral structure, or in other words the anatomic limitations inherent in this age. Normal transurethral resection devices for adults, which have a relative large caliber, may not be appropriate for children, and may even lead to urethral damage. In our study, transurethral resection was successfully performed by using the ureteroscope with holmium laser in the 11-year-old boy who could not benefit from the normal device of transurethral resection used in adults. Thus, we suggest that ureteroscope may be an appropriate alternative for urologists to remove the tumor.
in children.

To date, no standards exist for tumor surveillance strategies. Nevertheless, the majority of series described TCCB in young population had excellent clinical outcomes. In a few other studies, poor outcomes were also reported. On this basis, stricter follow-up with interval cystoscopy as the primary modality were recommended. However, cystoscopy is indeed inevitable in both confirming diagnosis and removing the neoplasms located in the bladder. The invasive characteristic together with the requirement of general anesthesia limits its use as a method for tumor surveillance. The invasive characteristic together with the requirement of general anesthesia limits its use as a method for tumor surveillance in this young population. Considering the high efficiency of bladder ultrasound in detecting intravesical lesions and the infrequency of recurrence of low-grade TCCB, Hoenig and colleagues suggest urinalysis and bladder ultrasound to be the appropriate screening means for low-grade TCCB instead of cystoscopy. Similarly, Bujons and colleagues who carried out a long-term follow-up of pediatric TCCB patients, encourage bladder ultrasound to be used in screening children, especially for follow-up in the mid and long term, while a decreased use of cystoscopy was also recommended. In our series, where all patients were assigned as LGUC, urinalysis and bladder ultrasound were chosen as the primary methods in the surveillance protocols, with neither recurrence nor progression during the follow-up, suggesting that bladder ultrasound is useful in screening the pediatric TCCB patients, especially for those with low-grade nature. Moreover, further studies are needed to identify under what circumstances we should use an aggressive screening protocol, or follow the high-grade cases aggressively by increased use of cystoscopy.

In conclusion, TCCB is an extremely rare entity with less aggressive behavior in the pediatric population. In order to prevent urethral damage, we recommend an ureteroscope, the caliber of which is smaller, as an appropriate alternative for urologists to remove the tumor in children. Bladder ultrasound presents as an efficient method in screening pediatric TCCB patients, especially for those of low-grade nature.

References