Case Report

A case in which bladder cancer invaded the ureteral orifice and was resected via photodynamic diagnosis-assisted transurethral resection involving orally administered 5-aminolevulinic acid

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Abbreviations & Acronyms
5-ALA = 5-aminolevulinic acid
BCG = Bacillus Calmette–Guérin
CT = computed tomography
MRI = magnetic resonance imaging
NMIBC = non-muscle invasive bladder cancer
PDD = photodynamic diagnosis
SIMC = Saitama Medical University International Medical Center
TUR-BT = transurethral resection of bladder tumor

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Introduction: Transurethral resection of bladder tumor is widely used in combination with photodynamic diagnosis to treat non-muscle invasive bladder cancer. We experienced an intriguing case, in which bladder cancer infiltrated into the right ureteral orifice and was resected via photodynamic diagnosis-assisted transurethral resection involving the oral administration of 5-aminolevulinic acid.

Case presentation: This case was a 71-year-old Japanese man. He was diagnosed with bladder carcinoma, which had infiltrated into the right ureter (clinical classification: T1, N0, M0). He underwent transurethral resection involving the oral administration of 5-aminolevulinic acid. We successfully resected the tumor in the ureteral orifice, which was accomplished by resecting the ureteral orifice until the non-luminescent lumen was exposed. After the surgery, to prevent recurrence, Bacillus Calmette–Guérin was administered intravesically after right ureteral stent placement.

Conclusion: Photodynamic diagnosis-assisted transurethral resection involving the oral administration of 5-aminolevulinic acid has the potential to treat ureteral tumors derived from bladder tumors.

Key words: 5-aminolevulinic acid, photodynamic diagnosis, transurethral resection of bladder tumor, urothelial carcinoma.

Keynote message

We experienced an intriguing case, in which bladder cancer infiltrated into the right ureteral orifice and was resected via PDD-assisted TUR (PDD-TUR-BT) involving the oral administration of 5-ALA (oral-PDD-TUR-BT). It is assumed that if the aminolevulinic acid had been administered intravesically, then it would not have been possible to visualize the tumor in the ureteral orifice. Based on the current report, oral-PDD-TUR-BT may be an effective treatment for bladder carcinoma that has infiltrated into the ureteral orifice. It is desirable that oral-PDD-TUR-BT is approved as a treatment for bladder carcinoma outside of Japan.

Introduction

In recent years, TUR-BT has been widely used in combination with PDD (PDD-TUR-BT) to treat NMIBC.[1–4] According to guidelines issued in 2018 by the European Association of Urology and the National Comprehensive Cancer Network, PDD-TUR-BT involving the intravesical injection of an aminolevulinic acid, that is either 5-ALA or hexaminolevulinic acid, is recommended for NMIBC. The PDD-TUR-BT procedure performed in Japan involves the oral administration of 5-ALA (20 mg/kg, oral-PDD-TUR-BT).[1] It is unclear whether the oral or intravesical administration of 5-ALA is better for NMIBC; however, the oral administration of 5-ALA must be superior to the intravesical administration of 5-ALA for tumors in

the ureteral orifice because intravesically administered 5-ALA would not reach such tumors without vesicoureteral reflux. Here, we experienced an intriguing case, in which bladder cancer invaded the ureteral orifice and was resected via oral-PDD-TUR-BT.

Case presentation

The case we present was a 71-year-old Japanese man. When he was being treated for pneumonia at another hospital, CT image incidentally revealed a BT and mild right-sided hydronephrosis (Fig. S1) without metastasis. After his pneumonia had been cured, the patient was referred to the SIMC to receive treatment for his BT (SIMC-Uro# 11116, a unique non-sequential patient control number issued at the Department of Uro-Oncology, SIMC). At his first visit, the patient's physical (height: 1.56 m, weight: 48.9 kg) and routine laboratory data were within the normal ranges. He had been diagnosed with diabetes mellitus, which required regular insulin injections. MRI showed many BTs (Figs S2–S4). The largest tumor detected on MRI is indicated by the blue arrowhead in Figure 1a. The tumor indicated by the yellow arrowhead was observed as it progressed between the right ureteral wall (white arrowhead in Figure 1a) and bladder wall (red arrowhead). Moreover, a tumor was found within the right orifice of the ureter (green arrowhead), which had presumably caused the mild right-sided hydroureter ("u" in Figure 1a, see also Figures S1–S4). Thus, the patient was diagnosed with bladder carcinoma, which was suspected to have infiltrated into the ureter (green arrowhead). No apparent muscle invasion, lymph node metastasis, or distant metastasis was observed (clinical classification: T1, N0, M0, according to the classification of the Union for International Cancer Control).

The patient underwent oral-PDD-TUR-BT (20 mg/kg of 5-ALA was administered 2 hours before surgery) using the D-LIGHT system (Table 1). As suggested by MRI (blue arrowhead in Figure 1a), the main papillary tumor was located on

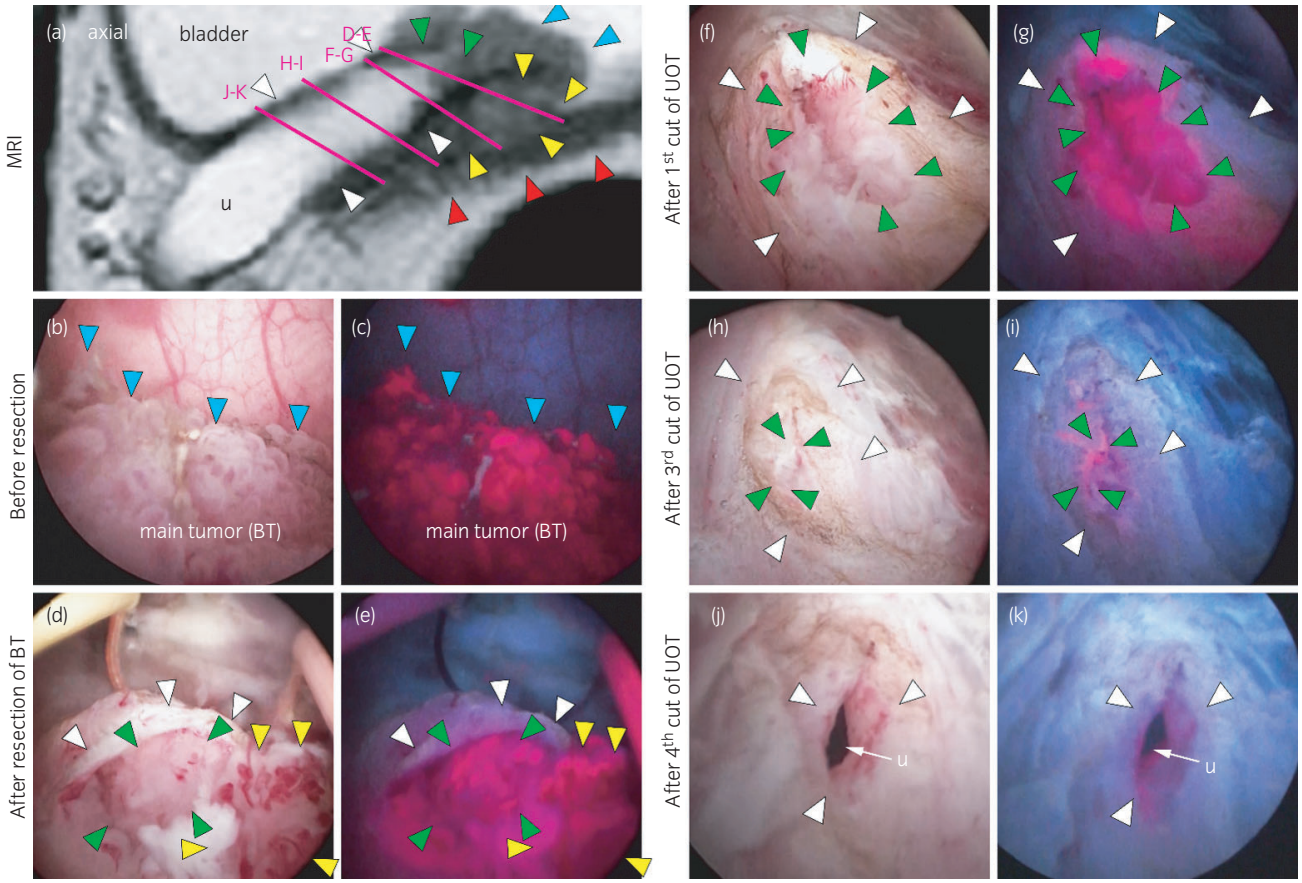

Fig. 1 The blue arrowhead indicates the main BT. The yellow arrowhead indicates the BT between the right ureter and bladder wall. The green arrowhead indicates the tumor in the ureter. The white arrowhead indicates the edge of the ureter. The pink lines indicate the resection lines for each phase (e.g. lines D and E correspond to Figures d and e, respectively). (a) A T2-weighted MRI image. (b) The main tumor under white light (at 0 s in Video S1). (c) The main tumor under blue light (the same tumor as is shown in panel b) (at 1 s in Video S1). (d) The tumor in the right ureteral orifice after the main BT had been resected (at 4 s in Video S2). (e) The tumor in the right ureteral orifice under blue light (the same tumor as is shown in panel d) (at 3 s in Video S2). (f) The papillary tumor in the dilated right ureteral orifice after the first resection procedure (at 9 s in Video S2). (g) The tumor in the right ureteral orifice under blue light (the same tumor as is shown in panel f) (at 12 s in Video S2). (h) The tumor in the right ureter after the third resection procedure (at 9 s in Video S3). (i) The tumor in the right ureter under blue light after the third resection procedure (the same tumor as is shown in panel h) (at 11 s in Video S3). (j) The right ureter after the fourth resection procedure (at 7 s in Video S4). (k) The right ureter under blue light after it had been resected (the same tumor as is shown in panel i) (at 8 s in Video S4). U, ureter.

Table 1 Instruments of the D-LIGHT system

Components	Model number
Image S HX-P FI	KTH113
Image1S X-Link	KTC301
D-Light C/AF	K20133601-3
26 full HD monitor	K9826NB-JP
Autocon III 400	KUH400U
Hopkins forward – oblique telescope 30°	K27005BIA
Working element	K27040EB
Resect-scope sheath	K27040SL K27040XA
Obturator of the sheath	K27048CK
Biopsy forceps	K27072BL
Adaptor	K27094BY
Light cable	K495FS
Bipolar cord	KUH801
KARL STORZ SE & Co., Tuttlingen, Germany	

the right ureteral orifice (blue arrowhead in Figure 1b), and it clearly emitted fluorescence under blue light (Fig. 1c). It had invaded the bladder neck, the prostatic urethra, and the right posterior wall of the bladder (Video S1). In addition, three daughter tumors were found on the posterior wall of the bladder (Video S1). Random bladder biopsy samples were obtained from the surrounding normal tissue (the posterior, left, and right walls) and the tumor-infiltrated tissue (the bladder neck and prostatic urethra). Subsequently, we deeply resected the largest tumor (Fig. 1b,c). The right ureteral orifice was exposed, and it was found to have been blocked by papillary tumors (the tumors in the ureter and the ureteral wall are indicated by green and white arrowheads, respectively; Fig. 1d,e). We deeply resected the tumors in the ureteral orifice; however, after the resection procedure residual tumors were identified within the ureteral orifice (green arrowhead in Figure 1f), which emitted potent fluorescence under blue light (Fig. 1g, see also Video S2). We decided to attempt to remove the remaining tumors. After the second and third attempts to resect the ureteral tumors (deep resections, Video S3), no tumors were visible under white light in the right ureter (Fig. 1h); however, marked fluorescence was observed from the ureteral mucosa (Fig. 1i), which was indicative of residual cancer. If the patient had undergone TUR without PDD, we would have finished the surgery at this point. Instead, we performed a biopsy of the fluorescence-emitting tissue. We then attempted to remove the suspected residual carcinoma. After the fourth resection of the ureteral orifice, the hydroureter-affected lumen was exposed, the mucosa of which was smooth and did not emit fluorescence (Fig. 1j,k). Subsequently, we performed a biopsy of the ureteral mucosa (Video S4).

The pathological diagnosis of the BT was low-grade urothelial carcinoma, which had not invaded the muscular layer (pTa). No cancer cells were detected in random biopsy specimens. As expected from the PDD, low-grade cancer cells were detected in the ureteral mucosa after the third resection of the ureteral orifice, in which an irregular and fluorescent mucosa was identified (Fig. 1h,i). On the other hand, no cancer cells were found in the smooth and non-fluorescent mucosa after the fourth resection procedure. To prevent tumor recurrence, the patient is currently being treated with intravesically administered BCG via a right ureteral stent, which exposes both the ureter and the bladder to BCG. We concluded that the ureteral tumor was a BT that had infiltrated into the ureter because (i) preoperative MRI (Fig. 1a) showed that the main tumor was located in the bladder, (ii) the hydronephrosis was mild (CT findings, Figure S1; the hydronephrosis would have been severe if the ureteral tumor had originated from the ureteral orifice), and (iii) the pathological analyses did not show muscular invasion. Thus, we succeeded in resecting the tumor in the ureteral orifice, which was accomplished via PDD using orally administered 5-ALA.

Discussion

Herein, we reported a case, in which a BT that had invaded the ureteral orifice was resected via PDD-TUR-BT involving the oral, rather than intravesical, administration of 5-ALA. In Japan, oral-PDD-TUR-BT was approved by the Ministry of Health, Labor, and Welfare in December 2017 based on several clinical trials, which demonstrated the safety and effectiveness of oral-PDD-TUR-BT.[5,6] It has been reported that PDD exhibits sensitivity and specificity of 79.6% and 80.6%, respectively, for detecting NMIBC.[1] In addition, luminescence is frequently detected when PDD is used to examine tangential tissue walls and inflamed tissue at sites affected by bladder cancer.[7–9] BT-derived ureteral tumors that are similar to those seen in the present case might be resected under ureteroscopy.[10] Otherwise, partial ureterectomy or radical nephroureterectomy, which are more invasive procedures, are required for curative treatment. In conclusion, our experience indicates that oral-PDD-TUR-BT has the potential to treat BT-derived ureteral tumors in the ureteral orifice that exhibit the MRI findings shown in Figure 1a.

Conflict of interest

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. CT imaging (axial).
Figure S2. T2-weighted MRI imaging (axial).
Figure S3. T2-weighted MRI imaging (coronal).
Figure S4. T2-weighted MRI imaging (sagittal).
Video S1. BTs before resection.
Video S2. Right orifice (first resection procedure).
Video S3. Right orifice (second and third resection procedures).
Video S4. Right orifice (fourth resection procedure).

Editorial Comment

Editorial Comment to A case in which bladder cancer invaded the ureteral orifice and was resected via photodynamic diagnosis-assisted transurethral resection involving orally administered 5-aminolevulinic acid

Watanabe *et al.*[1] reported an interesting case of bladder cancer in the intramural ureter exhibiting red fluorescence with the use of orally administered 5-aminolevulinic acid-mediated photodynamic diagnosis (ALA-PDD). The tumor was resected with negative margins, which did not show red fluorescence by ALA-PDD. The present study reports that an exact diagnosis and precise resection of the bladder tumor in the intramural ureter are possible with the use of ALA-PDD. Faba *et al.*[2] reported a good oncological outcome for conventional transurethral resection of bladder cancer without T1 or carcinoma *in situ* in the intramural ureter. ALA-PDD can be considered in patients suspicious for bladder cancer in the intramural ureter, though long-term follow-up for local or upper urinary tract recurrence is needed in the present case, and accumulating information on such cases is necessary.

False-positive results should be noted during ALA-PDD for bladder cancer.[3] Oblique illumination and inflammation can lead to false-positive results, which are often observed at the bladder neck, trigone, and around the orifice.[4] Because ureteral stenosis can occur after resection of the orifice (11.6%),[2] unnecessary surgery should be avoided. Draga *et al.*[5] reported that the learning curve for surgeons performing transurethral resection under PDD was proportional to the decrease in the number of false positives up to 12–18 months after the initial PDD procedure. Thus, some experience with ALA-PDD and careful observation are necessary to perform ALA-PDD for bladder tumors in the intramural ureter.

The present case also reveals the potential of ALA-PDD for diagnosis of upper urinary urothelial carcinoma (UTUC). Kata *et al.*[6] reported the potential of ureteroscopy using 5-ALA, and that ALA-PDD for UTUC can identify tiny lesions and carcinoma *in situ*, which is missed under conventional white light. 5-ALA can be administered using either an oral or transurethral route. On the other hand, hexaminolevulinate, which is used in Europe for PDD of non–muscle-invasive bladder cancer, is administered via intravesical instillation only. Therefore, ALA-PDD is a promising diagnostic tool for various kinds of cancers including UTUC, and trials of ALA-PDD in the treatment of such cancers are being performed.

The use of ALA-PDD for bladder cancer has recently been approved in Japan and performed in various institutions. We should report the effectiveness of ALA-PDD from Japan, and transurethral resection with ALA-PDD should be approved as a treatment for bladder carcinoma outside of Japan as emphasized by Watanabe *et al.* in their keynote message.

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Conflict of interest

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