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Clinical Trial for Preoperative Diagnosis of Locally Advanced Invasive Ureteral Cancer

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Locally advanced invasive ureteral cancer causes poorer prognoses compared with organ confined cancer. Preoperative diagnoses of locally advanced invasive cancer are controversial and not established in the detail method. It is important to investigate the possibility of preoperative diagnosis of locally advanced invasive ureteral cancer for the decision of the performance and the appropriate regions of lymph node dissection during surgical treatments.

Eight patients who underwent surgical management of ureteral cancer were selected for this study in our institution. We compared the preoperative diagnoses about their invasiveness and progression of ureteral cancer by the combination of computed tomography, ureterography, and urine cytology, with the postoperative pathological diagnoses.

Our preoperative diagnoses about their invasiveness and progression showed that 2 out of 8 cases were locally advanced invasive cancer, 5 out of 8 cases were organ confined, and 1 out of 8 cases had the possibility of locally advanced invasive cancer from the combined findings of computed tomography, ureterography, and urine cytology. From the pathological investigation after surgical managements, of the 8 cases, 5 were diagnosed as organ confined ureteral cancer, 2 were locally advanced invasive cancer, and 1 was organ confined with locally advanced invasive character. These pathological diagnoses were, in most cases, corresponded with our preoperative diagnoses regarding their invasiveness and progression.

We demonstrated the possibility to distinguish preoperatively locally advanced invasive ureteral cancer and organ confined ureteral cancer in most cases with the combined testings of computed tomography, ureterography, and urine cytology for the decision about the surgical technique and the performance and the ranges of lymph node dissection.

Radical nephroureterectomy has been the gold standard in the treatment of ureteral cancer and is warranted for patients with high grade and invasive disease that is organ confined or is only locally advanced (1). The decision of performance and appropriate regions of lymph node dissection for surgical technique remains controversial. The positive urine cytology of ureteral cancer is generally considered to have higher ratio in high-grade and non-papillary tumors. Such high-grade, high-stage, and non-papillary cancer has greater potentials of being invasive cancer. However, organ-confined ureteral cancer may be

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considered to remain inside ureteral wall and have no invasion to other tissues or organs and no metastasis. The locally advanced invasive ureteral cancer which is known to invade to periureteral tissue causes poorer patients' prognoses and easily progresses to lymph node and metastasizes to other organs. The literature review said that 5-year survival of the patients with T3 tumor has worse (16-33 %) than those patients with T2 tumor (43-75 %) in upper urinary tract urothelial tumors (1).

Regarding the preoperative detection of invasive ureteral cancer, many authors have reported that ureteral cancer that is undetectable in the imaging results may be found by urine cytological testing (2-4). Radiological studies report that the preoperative diagnosis regarding the extent of tumor invasiveness is not very accurate from magnetic resonance imaging (MRI) results (5, 6).

In the current study, we attempted to find the possibility of locally advanced invasive ureteral cancer preoperatively from the combination of imaging findings, such as CT, ureterography, and urine cytology testing. We expect this preoperative detection of locally advanced invasive ureteral cancer to provide important information for better patients' prognoses in order to decide the details of surgical management such as the performance and the region of lymph node dissection.

PATIENTS AND METHODS

Eight patients who underwent surgical management of ureteral cancers were selected for this study in our institution from August 2000 to July 2001. We performed CT and ureterography for all of these patients and classified their ureteral tumors as having irregular wall thickening or intraluminal masses. We used MRI diagnosis supplementally. Urine cytologies including collected ones from ureteral catheter were tested in all those patients. In this study, according to the TNM classification of Hermanek et al., we defined in this study locally advanced invasive cancer as the cancer which invades to periureteral tissue (T3) and organ confined cancer as the cancer which is papillary noninvasive carcinoma (Ta) or carcinoma in situ (Tis) or the tumor invaded to superficial connective tissue (T1) or the tumor invaded to the lumina muscularis (T2) because T3 tumor causes worse patients' prognosis than those patients with T2 tumor as mentioned in the introduction section (7). All of our cases are transitional cell carcinoma (TCC) in ureter; therefore, we term it as ureteral cancer in this study.

After October 2000, we performed multi-slice CT and obtained images in the three phases (plain phase, enhanced early phase, and enhanced late phase). A single pathologist examined the urine cytology and defined class IV and class V results as a positive finding. Those patients who had lymph node or other organ metastasis were excluded from this study. Preoperative decision of locally invasive cancer or organ-confined cancer was made from the results of the imaging studies and urine cytology. We performed surgical management for all of the patients selected in this study.

All of the tumors diagnosed preoperatively as locally advanced invasive cancer or suspicious locally advanced invasive cancer were located in the lower portion of ureter, and therefore, we performed nephroureterectomy with wide resection of the intra-pelvic lymph nodes (common iliac, external iliac, internal iliac, obturator, and pre-sacral lymph nodes).

In the cases that were diagnosed preoperatively as organ confined cancer, we performed conventional nephroureterectomy and sampling resection of the attending lymph node. A single pathologist performed the pathological tests and the postoperative diagnoses. We then compared the preoperative diagnoses with the postoperative pathological diagnoses in each case.

Generally, we obtained the informed consents from the patients that the results of the testings performed routinely can be materials for clinical studies or case reports under the situation that the personal information is kept inside our institution.

RESULTS

Preoperative diagnoses about the locally advanced invasive cancer and organ confined cancer and postoperative pathological diagnoses are shown in Table 1. We showed ureterography and CT findings in organ confined ureteral cancer and locally advanced invasive ureteral cancer (Figure 1: organ confined ureteral cancer, the case 7 in Table 1, Figure 2: locally advanced invasive ureteral cancer, the case 1 in Table 1). In our cases, regarding the urine obtained by ureteral catheter, 4 out of 8 ureteral cancers had positive urine cytology and 2 out of 3 locally advanced invasive cancers had positive urine cytology.

Our ureterography results showed that 5 out of 8 cases had the finding of intraureteral tumor and 2 out of 8 revealed the possibility of locally advanced invasive cancer but also left the possibility of other diseases outside ureter, and 1 out of 8 was undetectable. Our CT results also showed 5 out of 8 cases had the finding of intraureteral tumor and 2 out of 8 revealed the possibility of locally advanced invasive cancer but also left the possibility of other diseases which cause the thickness of ureteral wall because the findings of those 2 cases were not typical locally advanced invasive cancer, and 1 out of 8 was undetectable. In the combination of the findings from cytology, ureterography, and CT, we diagnosed preoperatively about their invasiveness and progression that 2 out of 8 cases were locally advanced invasive ureteral cancer, 5 out of 8 cases were organ confined ureteral cancer, and 1 out of 8 cases had a possibility of locally advanced invasive ureteral cancer.

In the postoperative pathological results, of the 8 cases, 5 were diagnosed as organ confined, 2 were locally advanced invasive, and one was organ-confined cancer with partially local advanced invasive character. Our preoperative diagnoses about cancer invasiveness and progression corresponded, in most cases, with the postoperative pathological diagnoses. Additionally, in our comparison of the preoperative diagnoses by CT alone with those by the combined testings (CT, ureterography, and cytology), the latter brought us better quality of preoperative diagnoses (at least 7 out of 8) than former (5 out of 8) in their accuracies.

Table 1. Patients' backgrounds and preoperative and pathological diagnoses

case	age/sex	Ureterography	Urine cytology*	Catheter	CT	Preoperative diagnosis	Pathological diagnosis
1	74/M	irregular stenosis	Neg	Neg	irregular thickness of whole ureteral wall	Possibility of locally advanced invasive cancer	Organ confined cancer with partly local advanced invasive character (TCC, G3, pT3, INFγ, pN2, ly0, v0)
2	54/M	intraureteral tumor	Neg	Neg	s/o intraureteral tumor	Organ confined cancer	Organ confined cancer (TCC, G1, pT1, pN0, ly0, v0)
3	75/M	intraureteral tumor	Neg	Neg	intraureteral tumor	Organ confined cancer	Organ confined cancer (TCC, G1, pT2, pN0, ly0, v0)
4	76/M	intraureteral tumor	Neg	Neg	intraureteral tumor	Organ confined cancer	Organ confined cancer (TCC, G1, pT2, pN0, ly0, v0)
5	72/F	undetectable (with stone)	Neg	Pos	thickness of ureteral wall	s/o** locally advanced invasive cancer	Locally advanced invasive cancer (TCC, G3, pT3, INFγ, pN0, ly1, v0)
6	80/F	irregular stenosis	Pos	Pos	undetectable†	s/o locally advanced invasive cancer	Locally advanced invasive cancer (TCC, G3, pT3, INFγ, pN2, ly2, v1)
7	72/M	occlusion (s/o intraureteral tumor)	Neg	Pos	intraureteral tumor	Organ confined cancer	Organ confined cancer (TCC, G2, pT1, pN0, ly0, v0)
8	74/M	occlusion (s/o intraureteral tumor)	Neg	Pos	intraureteral tumor	Organ confined cancer	Organ confined cancer (TCC, G2, pT1, pN0, ly0, v0)

*Urine cytology
Neg: Negative
Pos: Positive
Catheter: urine obtained by ureteral catheterization

**s/o: suspicious of

†undetectable because of the influence by the artifact from artificial caput exchange of ossis femoralis

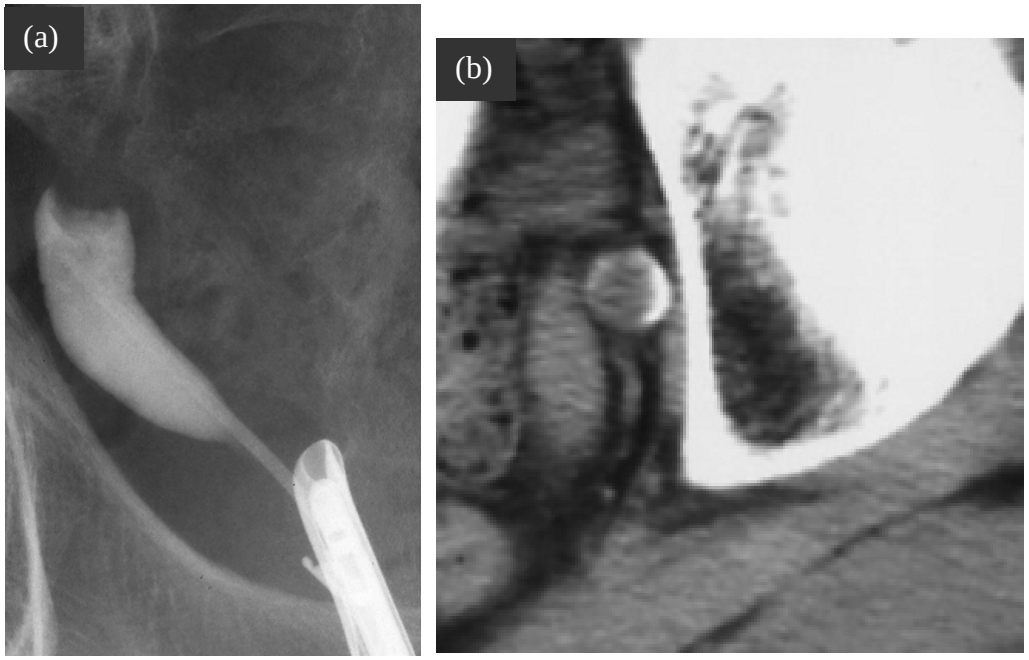

Figure 1. Retrograde ureterography (a) and CT (b) imaging of organ-confined ureteral tumor. Retrograde ureterography shows papillary tumor and CT imaging shows intraureteral tumor.

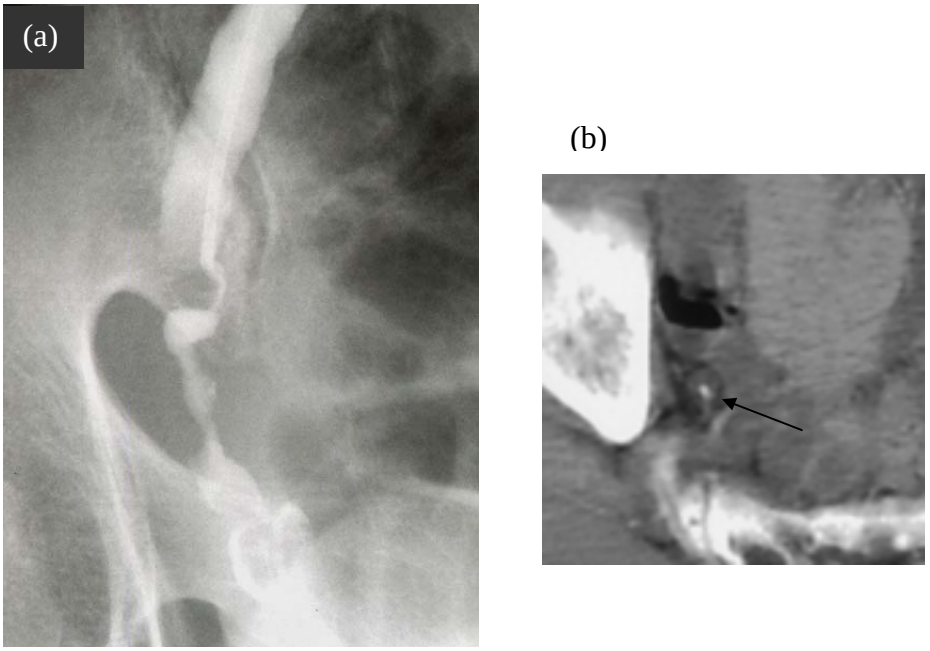

Figure 2. Retrograde ureterography (a) and CT (b) imaging of locally advanced invasive ureteral cancer. Retrograde ureterography shows irregular stenosis of ureter and CT imaging shows irregular thickness of ureteral wall (arrow).

DISCUSSION

The gold standard of surgical treatment of ureteral cancer has been generally considered to be radical nephroureterectomy. Recent reports indicate that partial ureteral resection or endoscopic resection of ureteral cancer is a treatment option for superficial tumor (8, 9). Performing lymph node dissection during the radical nephroureterectomy is generally considered to bring better prognoses in those patients in cases of locally advanced invasive cancer without lymph vessel invasion (10). However, the method of preoperative diagnosis for invasiveness and progression of tumor and determination of the performance and the appropriate region of lymph node dissection has not been clearly established. Therefore, we attempted the detection of locally advanced invasive ureteral cancer preoperatively for the decision of the appropriate surgical techniques and designs for the performance and range of lymph node dissection.

Recently, the imaging diagnoses by such as CT or MRI have made remarkable progression and the quality of imaging technique has been improved dramatically. Typical findings of ureteral cancer by CT are considered to be 1) soft tumor shadow which projects into the intra-ureteral space in the occlusive position of the ureter and 2) thickness of the ureteral wall (11). In addition, we often find a tumor shadow in periureteral adipose tissue, which means that the tumor might have invaded to the tissue outside of the ureter and is considered thus a locally advanced invasive cancer. Some authors have pointed out that there is a limit to the discrimination between superficial cancer and invasive cancer with CT alone (12-15). Plants et al. stated that CT did not detect 4 ureteral cancers and all of these cancers were diagnosed as pT1 or pT2 stage in their 28 cases of transitional carcinoma. In addition, they reported that the corresponded ratio of preoperative CT diagnoses with postoperative pathological diagnoses was 56 % (5 out of 9) in pT3 cases of ureter cancers and 37 % (7 out of 19) in pT1 or pT2 cases of renal pelvic cancers and concluded that there were 8 cases of under-staging pT1 or pT2 cancers by CT and 2 cases of under-staging pT3 cancers (14). McCoy et al. reported similar results, and therefore, we conclude that we need to diagnose comprehensively by considering several kinds of testings because it is impossible to diagnose preoperatively with high reliability using only CT (15).

Regarding the usefulness of MRI, the better quality of a contrast medium for MRI has given us its much better diagnostic potential for ureteral cancer. However, as well as CT, it has a limited ability to image spaces; therefore, it is not easy to diagnose the T stage correctly with MRI alone (5, 6). On the other hand, magnetic resonance urography (MRU) has become especially noteworthy for its high diagnostic ability (16). However, its spread and the extent of quality has a wide variety among hospitals. From these reasons including the limit of MRI diagnoses about the T stage of ureteral cancers as mentioned above, we designed our study and decided our study's protocol.

Conventional preoperative urine cytology remains important. Gonzalez-Peramato et al. studied the comparisons of preoperative urine cytology results and postoperative pathological diagnoses. They stated that urine cytology selectively obtained from the upper urinary tract with endoscopic techniques is a reliable method in the diagnosis of renal pelvis and ureteral neoplasias. Urine cytology has sensitivity close to 90 % and specificity between 98-100 % for carcinoma in situ and high-grade urothelial neoplasias, thus it can contribute to the therapeutic decision-making process in a very effective manner even though the results have been variable with a diagnostic accuracy between 23 % and 100 %. Despite its low sensitivity, it may be useful in the diagnosis of low-grade urothelial neoplasias when samples are selectively obtained by catheterization (2). All these reports were regarding the effectiveness of cytology on the diagnosis for ureteral cancer, not for the invasiveness and

progression of ureteral cancer. However, in our case 5 and 6, the results of cytology gave the important information of the malignant cell because the findings from CT and ureterography were not sufficient for exact diagnoses.

The diagnosis for ureteral cancer is usually made with ureterography like intravenous urography (IVU) or retrograde pyelography (RGP). The surface of a ureteral filling defect could be smooth, irregular or stippled (12). However, because there are many causes of radiolucent upper urinary tract filling defects, using IVU as a sole diagnostic tool is dangerous (17). Retrograde examination allows an evaluation of a non-functioning kidney which happens when the kidney is extensively invaded by tumor without associated hydronephrosis or renal vein involvement (12). However, ureterography has the limitation of demonstrating extension into periureteral fat or metastasis (18) and, in most cases, we could not diagnose from the finding of ureterography alone if the disease is from intraureter or extraureter when we obtained the finding from Figure 2-a. On the other hand, especially in ureteral confined cancer like in our most cases, ureterography showed the essential information for the exact diagnoses.

In conclusion, we could diagnose preoperatively the locally advanced invasive ureteral cancer in most cases with the combined testings of CT, ureterography, and urine cytology. The establishment of this study will give us not only the appropriate knowledge of disease progression but also the clue for more accurate surgical techniques and designs including the performance and the range of lymph node dissection for better patients' prognoses.

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