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Original Article

Analysis of treatment strategies for patients with obstructive renal failure caused by advanced cervical carcinoma after the failure of retrograde ureteral stent placement

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Abstract: Objective: To analyze treatment strategies for patients with advanced cervical carcinoma with obstructive renal failure after the failure of retrograde ureteral stent placement. Methods: We retrospectively analyzed 68 cases of advanced cervical cancer secondary with ureteral obstruction and had difficulty in indwelling retrograde ureteral stent in recent 7 years (from January, 2008 to June, 2013); after the treatments of hemodialysis, Percutaneous Nephrostomy (PCN) and laparoscopic bilateral cutaneous ureterostomy respectively, we analyzed the 24 h urine volume, renal function, electrolyte, QOL, further therapy for cervical cancer and 2-year survival rate of the patients. Result: One week after the treatments, by comparing 24 h urine volume and serum creatinine values, we found urinary diversion group (2124.8 ± 440.7 ml, 84.0 ± 16.5 ummol/L) was better than PCN group (1062.6 ± 231.1 ml, 197.8 ± 7.8 umol/L) and hemodialysis group (47.0 ± 26.0 ml, 225.4±23.4 umol/L) and the difference was statistically significant ($P < 0.05$). In the aspect of serum potassium, there was no significant difference between three groups ($P > 0.05$). The radical radiotherapy probability rate and survival period (18.3 ± 6.1 months) of urinary diversion group were better than that of the other two groups. The difference was statistically significant ($P < 0.05$). In the aspect of 2-year survival rate, urinary diversion group (48.0%, 12/25) was better than hemodialysis group (0%, 0/20), however, there was no statistical difference ($P < 0.05$) by comparing with the PCN group (21.7%, 5/23) ($P > 0.05$). In the aspect of quality of life after operation, the scores of urinary diversion group were distinctly better than the others. Conclusion: For the patients with ureteric obstruction caused by advanced cervical cancer and failed in ureteral stent placement, urinary diversion surgery should be considered with priority for those who could undergo general anesthesia and laparoscopic operation to effectively and thoroughly improve the renal function of patients with long-term stability; it could provide conditions for patients receiving combined treatment for advanced cervical cancer and prolong their survival period and quality of life. If the patient could not undergo general anesthesia and laparoscopic operation, unilateral PCN and hemodialysis could be used as a temporary treatment.

Keywords: Advanced cervical cancer, ureteric obstruction, renal dysfunction, laparoscopic cutaneous ureterostomy, percutaneous nephrostomy (PCN), hemodialysis, the treatment strategies

Introduction

The invasion and oppression of advanced cervical tumor could result in ureteral obstruction, uronephrosis, and even lead to insufficient renal function, and affect the quality of life and follow-up treatment of patients. Retrograde ureteral stent implantation is the most common way to remove ureteral obstruction [1, 2]. However, due to the particularity of ureteral obstruction in patients with advanced cancer, some patients have difficulty with ureteral stent placement, and they need further treatment [3]. As for the treatment of those patients, it is rarely reported in China or other countries, without protocols for clinical application, it is more relied on doctor's experience. Hemodialysis, percutaneous nephrostomy (PCN) and urinary

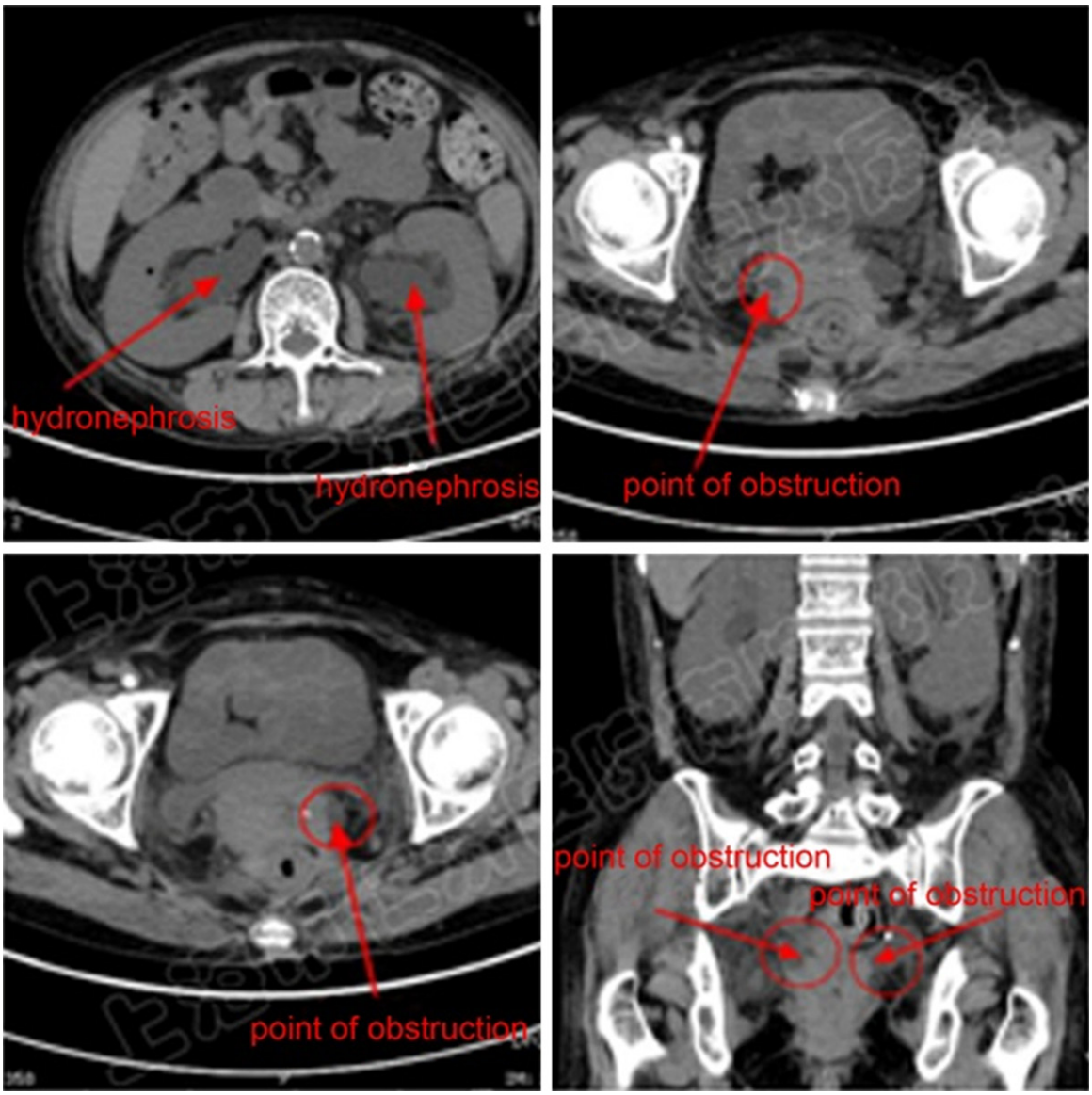

Figure 1. CT image of the patient with ureteric obstruction caused by advanced cervical cancer.

diversion, are commonly used in clinic. We have found that those three treatments had pros and cons. But for some patients, as long as treated with an appropriate strategy, they still have possibilities to restore renal function, improve the quality of life, and carry on further treatment for advanced cervical cancer, so as to prolong the survival period. We retrospectively analyzed the data of 68 patients with advanced cervical carcinoma and secondary obstructive renal failure after failed retrograde ureteral stent placement; we concluded the experience and explored the treatment strategies, as summarized below.

Material and methods

Subject

We retrospectively analyzed 224 cases of advanced cervical cancer carcinoma with secondary obstructive renal failure treated in the Department of urinary surgery in Renji Hospital Affiliated to Shanghai Jiaotong University School from January 2004 to June 2013. They were confirmed with squamous cell carcinoma by biopsy. All patients were treated with cystoscopic bilateral ureteral catheterization under local anesthesia. And a total of 68 cases of

Table 1. Comparison of general information

Index①	Urinary diversion group	PCN group	Hemodialysis group
	(n=25)	(n=23)	(n=20)
Ages/y	58.4±11.0	59.0±7.5	56.4±9.4
24 h urine volume/ml	91.6±64.9	95.2±66.7	63.0±45.6
Serum creatinin/umol/L	646.3±60.2	641.9±58.1	643.9±66.8
Serum potassium value/mmol/L	5.7±0.6	5.7±0.5	5.8±0.6
QOL score	36.6±3.6	36.2±3.4	37.1±3.1

Notes: ①The index groups were compared in pairs, P > 0.05.

patients, who were under 80 years with bilateral catheterization failure and blood potassium lower than 6.5 mmol/L, were enrolled in the study.

Clinical data

Among the 68 patients with advanced cervical cancer, 39 patients didn't receive any cervical cancer treatment (22 cases of stage IIIb, 17 cases of stage IVa), 11 patients had recurrence after radical radiotherapy, and 18 patients had recurrence after radical surgery; the patients aged from 42 years old to 76 years old with a median age of 56 years old, the average year was 58.0 ± 9.4 years old. In addition to many clinical manifestations of advanced cervical cancer, such as colporrhagia, fluid flow, pelvic pain, the patients also had similar symptoms of urinary system disease. Before admission, patients showed emergence of progressive oliguria for 10-14 days, with or without urine, and increased serum creatinine and serum potassium; pelvic CT or MRI examination showed that there was tumor invasion or ureteral stricture with different degrees of expansion on proximal end of ureter. See **Figure 1**.

All patients were evaluated for quality of life (QOL) after admission [4]. Cystoscopic examination showed vague ureteral opening that cannot be identified or bilateral ureteral opening. But the further ureteroscopic examination indicated that the external compression on distal ureter caused ureteral stricture, and ureteral catheterization was failed.

Serum creatinine, electrolytes, 24 h urine volume were reviewed before further treatment in all patients. We randomly selected treatment options: 20 patients were treated with hemodialysis (12 cases without treatment of cervical cancer, 4 cases with recurrence after radical operation and 4 cases with recurrence after radical radiotherapy); 23 patients received PCN puncture treatment (13 cases without treatment of cervical cancer, 6 cases with recurrence after radical operation, and 4 cases with recurrence after radical radiotherapy); 25 patients accepted laparoscopic bilateral cutaneous ureterostomy (14 cases without treatment of cervical cancer, 3 cases with recurrence after radical operation and 8 cases with recurrence after radical radiotherapy). The clinical data of the three groups were compared, and there was no significant differences, see **Table 1**.

Treatment method

The primary aim of obstructive nephropathy treatment is to rapidly restore kidney function of patients. We retrospectively analyzed three therapeutic strategies:

Hemodialysis group: fistulation of artery and vein was performed on the upper limb of patients for intubation to directly carry on regular hemodialysis treatment (on Monday, Wednesday, Friday, every week).

PCN group: based on pre-operative CT results and combined with color Doppler ultrasound reports, renal puncture was performed on the side with thicker renal parenchyma. F8-10 disposable puncture set was used to carry out PCN drainage under B-ultrasound localization.

Urinary diversion group (laparoscopic bilateral cutaneous ureterostomy): laparoscopic bilateral cutaneous ureterostomy was performed under general anesthesia after excluded the anesthesia risks by anesthetist.

Treatment of cervical cancer: after renal function improved, the general condition of patients was assessed to exclude radiotherapy taboos like uremia, myelosuppression, acute pelvic inflammatory disease ect. According to Cockcroft Gault formula, we calculated the endogenous creatinine clearance rate. For those patients with normal renal function or patients

Table 2. Comparison of clinic index between pre and post treatment by three techniques

Index	Urinary diversion group		PCN group		Hemodialysis group	
	Pretreatment	1 week after treatment	Pretreatment	1 week after treatment	Pretreatment	1 week after treatment
24 h urine volume①/ml	91.6±64.9	2124.8±440.7②	95.2±66.7	1062.6±231.1②	63.0±45.6	47.0±26.0
Serum creatinin①/umol/L	646.3±60.2	84.0±16.5②	641.9±58.1	197.8±7.8②	643.9±66.8	225.4±23.4②
Serum potassium value①/mmol/L	5.7±0.6	3.6±0.4②	5.7±0.5	3.6±0.5②	5.8±0.6	3.9±0.2②

Notes: ①The comparisons of the index 1 week after treatment between groups, $P < 0.01$; ②The comparisons of index before and after treatment in each group, $P < 0.01$.

at pre-uremic phase with insufficient renal function (ccr > 25 ml/min), we implemented radical radiotherapy; 6MV- X-ray pelvic external irradiation and ^{192}Ir intracavitary radiotherapy was applied on patients, who were initially treated, with radical radiotherapy dosage - A point (2 cm above the external cervix orifice, 2 cm paraxial to central axis of uterus) with dose of 70 Gy/8 weeks, B point (the same level with A point, 5 cm paraxial to central axis of uterus) with dose of 50~55 Gy. Three-dimensional conformal external irradiation and intracavitary brachytherapy were used for patients with recurrence after radical surgery. The dose was 55~60 Gy. For those patients with recurrence 2~3 years after radical radiotherapy: intracavitary brachytherapy was mainly used for the recurrence in central cervix with A point dose of 45~50 Gy; conformal external irradiation was mainly used for the recurrence on pelvic lymphnodes and parametrium with a target dose of 45~50 Gy. Within 2 years after radical radiotherapy, the recurrence was no longer treated with radiotherapy; instead, supportive treatment was adopted according to symptoms.

Research contents

We analyzed and compared the improvement of renal function before and after treatment in three groups, including 24 h urine volume changes, serum creatinine change and serum potassium change.

We analyzed and compared the condition after treatment in three groups of patients, including whether patients obtained further treatment for advanced cervical cancer, and whether the survival period was prolonged (from the day of surgery or the first time of hemodialysis to the day of death or end of follow-up).

We compared the postoperative QOL in three groups of patients according to the standard enacted in 1990, and re-evaluated one week after the treatment. The full score of QOL is 60 points, < 20 points means extremely poor, 21-30 points means poor, 31-40 points means moderate, 41-50 points means well, and 51-60 points means good.

Follow-up data

One week after surgery or first hemodialysis, all patients were examined for renal function, electrolyte and 24 h urine volume; one month after surgery or hemodialysis, we examined patients again to decide whether to proceed with further radiotherapy of cervical cancer; the follow-up method was telephone in combination with outpatient to inquiry the condition of patients and carry on relevant inspection. Follow-up interval was once a month by telephone after surgery, and every three months for an outpatient visit. 68 patients were followed up for two years without dropping case except for death.

Statistical analysis

Statistical analysis was performed using SPSS22.0 software, measurement data between groups was analyzed by univariate analysis; measurement data in groups was analyzed by paired t test, enumeration data among groups was tested by χ^2, $P < 0.05$ showed statistically significant.

Results

Metabolic index comparison

After 1 week of hemodialysis applied on 20 patients in this study, the 24 h urine volume was not significantly increased ($P > 0.05$), but the serum creatinine and serum potassium were significantly decreased, compared with the value before treatment, there were significant differences ($P < 0.05$) (see **Table 2**). However, patients had to maintain the dialysis for 2-3 times a week, otherwise creatinine

Table 3. Comparison of the further therapy for cervical cancer

	Urinary diversion group	PCN group	Hemodialysis group
Radiation rate①	100% (25/25)	43.5% (10/23)	0% (0/20)
Survival period①/month	18.3±6.1	14.2±6.4	6.7±2.0
2-year-survival rate	48.0% (12/25)	21.7% (5/23)③	0% (0/20)②

Notes: ①Comparison between groups, P < 0.05; ②Comparison between urinary diversion group and PCN group, comparison between PCN group and Hemodialysis group, both P < 0.05; ③Comparison between Urinary diversion group and PCN group, P > 0.05.

Table 4. Comparison of QOL after treatment

	Urinary diversion group	PCN group	Hemodialysis group
QOL score①	42.6±1.6	39.5±3.6	19.4±1.0
Two score of QOL①	8.48±0.96	7.09±1.35	4.70±0.73

Notes: ①Comparison between groups, P < 0.05.

increased again. 23 patients with PCN and 25 patients with urinary diversion had polyuric period at different levels after surgery, and their serum creatinine and serum potassium were significantly decreased without rebound after continuous monitoring, the difference, compared with pre-treatment values, was statistically significant (P < 0.05) (see **Table 2**).

1 week after each treatment, the comparisons of metabolic indexes between three groups show as follow: urinary diversion group had the maximum 24 h urine volume and hemodialysis group had the minimum volume, the difference between the three groups was statistically significant (P < 0.05); as for serum creatinine value, the urinary diversion group was significantly better than the other two groups, the difference was statistically significant (P < 0.05), PCN group was superior to hemodialysis group and the difference was statistically significant (P < 0.05); However, there was no significant difference between the three groups in serum potassium (P > 0.05) (see **Table 2**).

Comparison of tumor treatment situation and the survival period

All 20 patients in hemodialysis group failed to receive a further radical radiotherapy (0%, 0/20), the survival period after dialysis was 10 months for the longest and 3 months for the shortest with a median survival time of 6 months, the average survival time was 6.7 ± 2.0 months, and 2 year survival rate was 0%. Among the 23 patients in PCN group, 10 patients received radical radiotherapy after surgery (43.5%, 10/23), 6 patients received chemotherapy but failed to complete the whole course, 7 patients did not receive radical radiotherapy, the survival period in PCN group was 24 months for the longest (till the end of follow-up) and 3 months for the shortest with a median survival time of 13 months, the average survival time was 14.2 ± 6.4 months, and 2 year survival rate was 21.7% (5/23). The 13 patients in urinary diversion group were all treated with radical radiotherapy (100%, 25/25), the postoperative survive period was 24 months for the longest and 8 months for the shortest with a median survival time of 18 months, the mean survival time in urinary diversion group was 18.3 ± 6.1 months, and 2-year survival was 48.0% (12/25).

Comparison of radiotherapy acceptance rate between the three groups showed urinary diversion group had the best treatment effect with PCN group followed and hemodialysis group the worst, the differences were statistically significant (P < 0.05). Comparison of 2-year survival rate between three groups showed urinary diversion group was better than hemodialysis group, but no statistical differences comparing with PCN group (**Table 3**).

Comparison of QOL

The results showed that the QOL score of patients in urinary diversion group was 40-45 points with a median score of 42 points. The average score wss 42.6 ± 1.6 points, ranked "well". The QOL of patients in PCN group was points with a median score of 39 points. The average score was 39.5 ± 3.6 points, ranked "General" or "better". QOL score of patients in hemodialysis group was 18-21 points with a median score of 19 points. The average score was 19.4 ± 1.0 points, ranked "extremely poor" and "poor". The differences between three groups were statistically significant (P < 0.05, **Table 4**).

In QOL score table, the comparison of the scores in two sub-items ("self-awareness of

cancer" and "attitude toward treatment") showed that urinary diversion group was significantly higher than PCN group and hemodialysis group, the differences were statistically significant ($P < 0.05$), and PCN group was higher than hemodialysis group, the difference was statistically significant ($P < 0.05$) (**Table 4**).

Discussion

Advanced cervical cancer complicated by ureteral obstruction can lead to renal insufficiency and even renal failure or infection, seriously affect the quality of life of patients and sometimes even threaten their life [5]. Ureteral stent implantation is a common surgical method to solve ureteral obstruction; however, some patients with ureteral obstruction induced by advanced cervical cancer often failed in ureteral catheterization due to the failure in finding the opening of ureter caused by tumor invasion on bladder or ureteral stricture caused by tumor compression [6-8]. The conditions of these patients are always more critical, hemodialysis or surgical treatments are required as soon as possible in order to quickly and safely relieve the symptoms [9].

Draining by nephrostomy and without considering of stricture of lower ureter, PCN surgery has become one of the preferred surgical treatments for urological surgeon [10]. Although PCN surgery can improve renal function, there is a potential risk of severe bleeding, drainage-tube came off and retrograde infections, also, it affects the sleep of patients [11], and it does not necessarily prolong survival time of patients [12]. Plesinac KV et al. [13] reported that 24.8% of patients restored renal function after PCN, among which only 36.7% of the patients were performed with bilateral PCN surgery and the rest were performed with unilateral surgery, 37.61% of the patients suffered drainage-tube came off after surgery and 19.6% of the patients suffered postoperative infection, the 2-year survival rate was only 16.8%. Urinary diversion surgery can also improve renal function without considering the obstruction, and has less impact on QOL of patients. However, Lapitan MC [14] reported there was no significant improvement in survival rate and QOL score in patients with advanced cervical cancer.

In this study, we found that hemodialysis alone or PCN alone did not improve the prognosis of patients. Hemodialysis treatment only improved renal function but failed to relieve obstruction; as a result, renal function recovery was not stable and the endogenous creatinine clearance rate was low (less than 25 ml/min), and patients could not be treated with further radiotherapy. Unilateral PCN partially relived ureteral obstruction, the urine volume increased significantly, but renal function wasn't completely recovered. Due the small size of drainage tube, it was easy to block or lose off, postoperative recurrence was likely to happen, so some patients still failed to carry on further radiotherapy. Urinary diversion completely solved the problem of ureteral obstruction, postoperative recovery was good and steady, and patients could receive radical radiotherapy better. The survival period of patients with advanced cervical cancer depends on the effect of radiotherapy or chemotherapy [16]. Therefore, by comparing the survival period of three groups, the urinary diversion group was significantly longer than the other two groups. PCN group was also better than hemodialysis group ($P < 0.05$).

Comparing the quality of life, the postoperative life quality in three groups all decreased. Because of abdominal wall stoma, infection caused by urine reflux and other reasons, the QOL of urinary diversion group decreased, however, the renal function recovery was better and stable in long-term that create conditions for radiotherapy, therefore, the QOL score was relatively higher and ranked "well", patients had a greater hope, thus the scores of "self awareness of cancer" and "attitude toward treatment" were higher. Although the renal functions were improved after operation in PCN group, regular replacement of the fistula tube and even re-puncture was required because the fistula tube was easy to clog, lose off and induce infection; if the puncture failed, patients should be treated by other methods, resulting in the uncertainty in postoperative treatment for advanced cervical cancer. As a result, the QOL score of PCN group was between "general" and "well", and the scores of "self-awareness of cancer" and "attitude toward treatment" were lower than that of urinary diversion group ($P < 0.05$); the QOL score of hemodialysis group was the lowest in three groups ($P < 0.05$), and it is

related with regular hemodialysis that patients could hardly carry on further radiotherapy.

In this study, in order to carry on further treatment for cervical cancer, 5 patients, out of the 23 cases in PCN group, underwent contralateral percutaneous nephrostomy on second phase (2 weeks after surgery) after been confirmed without obvious contraindications by urological surgeon. The postoperative 24 h urine volume and serum creatinine value of these 5 patients were similar to that of the urinary diversion group, and they were all performed with radical radiotherapy. Among them, 3 patients also had several times of unilateral drainage tube obstruction and replaced fistula tube; compared with unilateral PCN patients, the ureteral obstruction of patients with bilateral PCN surgery was solved more thoroughly, thus even if one drainage tube blocked after operation, patients wouldn't be disturbed with continuous radiotherapy. We performed QOL evaluation again on these 5 patients, and found the QOL score was decreased (Pre-operation: 39, 39, 37, 37, 37 vs. Post-operation: 33, 32, 31, 30, 30), mainly with the significant decrease in "spirit", "sleep", "treatment side effect", but there were a slight increase in "self-awareness of cancer" and "attitude toward treatment". So we think bilateral PCN can completely remove the ureteral obstruction, and its treatment effect should be close to that of laparoscopic bilateral cutaneous ureterostomy and better than unilateral PCN; but there are still some risks, such as tube replacement failure, puncture hemorrhage, drainage tube blockage and infection etc. Moreover, the bilateral PCN have greater impact on QOL of patients, its QOL score was lower than that of patients with laparoscopic bilateral cutaneous ureterostomy (need data replenishment due to small sample size).

Patients with advanced cervical cancer are often associated with anemia, malnutrition, hypoalbuminemia, cachexia, high difficulty and risk of surgical intervention [16]. Laparoscopic bilateral cutaneous ureterostomy, with advantages of small trauma, short operation time, can thoroughly solve ureteral obstruction and quickly relieve renal function insufficiency to create conditions for patients to accept further comprehensive treatment; however, this treatment requires patients to tolerate general anesthesia, and due to previous surgeries or radiotherapy, patients always have intestinal adhesions that requires high laparoscopic skill of the surgeon. Unilateral PCN can rapidly alleviate renal function of patients, but it requires patients be tolerant with prone position and requires normal blood coagulation function. Unilateral PCN cannot completely remove ureteral obstruction, to reduce the risk of hemorrhage. Unilateral PCN often chooses F8-F9 micro channel, which is smaller in lumen and easy to clog. Bilateral PCN on second phase can better solve these problems and reduce the risk of renal failure caused by drainage tube obstruction; however, most of these patients are with chronic obstructive disease and less hydronephrosis, PCN puncture is difficult and requires high skills in B ultrasound localization and puncture of the surgeon; furthermore, secondary surgery has high risks, such as hemorrhage and infection, and has great impact on the QOL of patients, thus the surgeons should fully assess the disease and well communicate with patients.

According to this study, we think the patients with advanced cervical cancer and secondary bilateral ureteral obstruction, who failed in conventional ureteral catheterization, should choose an appropriate treatment strategy according to their own condition. The common type of cervical cancer is squamous cell carcinoma, which is sensitive to radiotherapy; even the patients were diagnosed of advanced cervical cancer and secondary bilateral ureteral obstruction and failed in conventional ureteral catheterization, they still can prolong their survival time and improve the quality of life after active and proper treatment by urological and obstetrical surgeons. Therefore, for urological physicians, the treatment principle should be creating possibilities for patients to accept further treatment as much as possible, rather than simply alleviate renal function. The proposed treatment strategies are as follows: 1. After been evaluated by anesthetist, patients, who can tolerate general anesthesia and laparoscopic surgery, should consider urinary diversion with priority to effectively and thoroughly improve renal function with long-term stability, and to create conditions for the further comprehensive treatment of cervical cancer and prolong the survival time and quality of life. 2. For the patients with poor conditions and cannot

tolerate general anesthesia or laparoscopic surgery, they should first consider unilateral PCN; a new round comprehensive assessment should be carried out after renal function and basic situation improved; patients could choose urinary diversion surgery or bilateral PCN according to the technical characteristics of surgeon, to create conditions for the further treatment of advanced cervical cancer. 3. For the patients with very bad conditions ($K^+ \geq 6.5$ mmol/L, 24 h urine volume ≤ urine continued for more than 24 hours) and couldn't tolerate with above two surgeries, they should first consider hemodialysis to save life, and after the renal function and basic condition stabilized, patients should be comprehensively evaluated again, and choose urinary diversion surgery or bilateral PCN according to the technical characteristics of surgeon to create conditions for further treatment.

Disclosure of conflict of interest

None.

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