Title: Management of ureteral obstruction in advanced testicular tumor with lymph node metastasis

Atsushi Ikeda[1], Koji Kawai[1], Satoshi Ando[1], Takehiro Oikawa[1], Hiromu Inai[2], Tomokazu Kimura[1], Ei-ichiro Takaoka[1], Takayuki Yoshino[1], Takahiro Suetomi[1], Takahiro Kojima[1], Jun Miyazaki[1], Hiroyuki Nishiyama[1#]

Author affiliations

[1] Department of Urology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575

[2] Department of Urology, International University of Health and Welfare Hospital, 537-3 Iguchi, Nasushiobara, Tochigi 329-2763

Running title: Ureteral stent for advanced testicular tumor with hydronephrosis

#Corresponding author

#Hiroyuki Nishiyama, Department of Urology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. Tel/Fax +81-29-853-3223, E-mail: nishiuro@md.tsukuba.ac.jp

Conflict of Interest: The authors have no conflict of interest to declare

Total number of figures and tables: 1 figure and 3 tables

Abstract

Objectives

Ureteral obstruction is one of the complications of testicular tumor with retroperitoneal lymph node (RPLN) metastasis that requires ureteral stenting for management. We elucidated the clinical courses of ureteral obstructions and changes in renal functions in patients with indwelling ureteral stenting.

Patients and Methods

The medical records of 56 patients who were treated for metastatic testicular tumors by chemotherapy at a single institute between 2002 to 2010 were retrospectively reviewed.

Results

Among 56 patients, 12 patients needed ureteral stenting before chemotherapy. The proportion of patients requiring ureteral stenting was significantly higher in seminoma than non-seminoma (47% and 12%, respectively, $P<0.05$). The ureteral stent was removed after chemotherapy or retroperitoneal lymph node dissection (RPLND) in all patients, except for one patient who died of cancer during chemotherapy. At RPLND, ureters were spared in three patients, a partial ureterectomy was needed in one patient, and

no case underwent adjunctive nephrectomy. These 11 patients presented no local and distant recurrence at median follow-up of 44 months. Ureteral stenting increased the estimated glomerular filtration rate to more than 60 ml/min before chemotherapy in all patients, but it decreased to less than 60 ml/min in six of 11 patients after chemotherapy.

Conclusion

Ureteral obstruction due to testicular tumor was relieved after chemotherapy or RPLND. Ureteral stenting was effective to improve renal function before chemotherapy, although we should pay special attention to deterioration of renal function during or after chemotherapy.

Mini abstract

The ureteral stenting is effective to manage the hydronephrosis of metastatic testicular tumor patients. But, attention should be paid to deterioration of renal function during or after chemotherapy.

Key words: ureteral stent, testicular tumor, retroperitoneal lymph node (RPLN), hydronephrosis, chemotherapy

Introduction

Testicular tumor is one of the common malignancies in young men and is well known as a rapidly progressive disease. Between 1980 and 1990, effective chemotherapy regimens including cisplatin against advanced testicular tumors were established. These chemotherapies and surgical interventions like retroperitoneal lymph node dissection (RPLND) achieved a high cure rate even in patients with multiple metastases. On the other hand, intensive chemotherapy with or without surgical treatment leads to several late sequelae in long-term testicular cancer survivors, and persistently impaired renal function is one of them (1-3).

The retroperitoneal lymph node (RPLN) is a common site of metastasis in advanced testicular tumors, and large metastases in RPLN occasionally lead to ureteral obstruction and resultant hydronephrosis (4,5). Ureteral obstruction and the resultant hydronephrosis may cause renal impairment and urinary tract infection during chemotherapy. Importantly, renal impairment limits delivery of adequate doses of anticancer drugs including cisplatin, which might result in a lower cure rate. Therefore, effective interventions to prevent ureteral obstruction are recommended in management of advanced testicular tumor (6).

Retrograde ureteral stenting is the most widely used initial treatment for malignant ureteral obstruction. Several investigators have described the efficacy and limitations of ureteral stenting for extrinsic ureteral obstruction due to pelvic malignancies such as gynecological cancer and colon cancer (7-9). These malignancies with ureteral obstruction due to metastasis are not curable, and generally ureteral obstruction progression follows disease progression. In contrast, ureteral obstruction should be relieved in patients with testicular tumor because most patients with advanced testicular tumor can be cured. However, the safety and efficacy of ureteral stenting during chemotherapy for advanced testicular tumor has not been well described. Also, it is not clear what proportion of patients can be stent-free after chemotherapy or will need adjunctive nephrectomy at RPLND due to resection of the ureter involved.

In this retrospective study, we reviewed our clinical experience with ureteral stenting in patients with advanced testicular tumor to elucidate how to manage ureteral obstruction and also examine the impact of ureteral stenting on renal function during and after chemotherapy.

Materials and Methods

Patients

A total of 56 advanced germ cell tumor patients were treated at Tsukuba University Hospital between June 2002 and August 2010. We retrospectively reviewed charts of these patients and identified 12 patients who underwent ureteral stenting for extrinsic ureteral obstruction due to retroperitoneal mass (Table 1). The median age at diagnosis was 39 years (range 26–58 years). They included 11 testicular tumor patients with RPLN metastasis and one retroperitoneal germ cell tumor patient. In 11 patients, retrograde ureteral stenting was performed before the start of chemotherapy. In the remaining non-seminoma patient, percutaneous nephrostomy (PCN) was initially required due to the inability to place a ureteral stent, but a ureteral stent was successfully placed after four courses of chemotherapy. A ureteral stent was placed in the left kidney in eight patients and the right kidney in five patients. One patient needed bilateral ureteral stenting.

Treatment for testicular tumors

Ten patients received a protocol consisting of bleomycin, etoposide, and cisplatin (BEP) (10) as the induction chemotherapy. Two patients who had risk

factors for bleomycin pneumonitis were treated with four courses of etoposide and cisplatin (EP). Dose reduction due to renal dysfunction was needed in four of 39 courses of induction chemotherapy. Postponements in the start of chemotherapy were observed in six of 27 subsequent treatment courses. The median duration of postponement was three days (1–6 days). In addition to the induction chemotherapy, six patients received second line or salvage chemotherapy for refractory or relapsed disease. The most frequently used second line chemotherapy regimen was paclitaxel, ifosfamide, and cisplatin (TIP) (11). Three patients needed a third line or further chemotherapy.

Principally, non-seminoma patients underwent surgical resection of residual operable masses when all tumor markers had normalized. However, surgery was omitted in seminoma patients with an adequately responding RPLN mass (less than 3 cm in diameter or negative FDG-PET scan), and they were followed closely. One non-seminoma patient underwent salvage RPLND under a tumor marker-positive and chemo-refractory condition.

Indication for and management of ureteral stenting

In principle, we adapted ureteral stenting when significant hydronephrosis

due to ureteral obstruction was identified. During chemotherapy, the ureteral stent was exchanged at least once every three months. At each ureteral stent exchange, retrograde pyelography was performed to assess ureteral obstruction. When ureteral obstruction was relieved, the ureteral stent was removed. In patients who underwent RPLND, the ureteral stent was removed after recovery from surgery.

Evaluation of renal function

The glomerular filtration rate (GFR) was estimated based on the serum creatinine concentration using the formula reported by Matsuo *et al*. (12). This equation originated from the Modification of Diet in Renal Disease (MDRD) study group (13), designed for Japanese individuals and recommended by the Japanese Society of Nephrology: eGFR (ml/min/1.73m^2) = 194 x serum Cr$^{-1.094}$ x age (years)$^{-0.287}$.

Statistical analysis

Differences in patient age and RPLN mass size between groups were analyzed by Student's *t*-test. Chi-square analysis was performed to compare

histology, risk category, and the proportions of seminoma and non-seminoma patients who underwent ureteral stenting. Pre-treatment eGFR were compared during and after treatment using 1-factor repeated measures ANOVA. A value of $P<0.05$ was considered statistically significant. Statistical analysis was performed using JMP software (version 9.02; SAS Institute Inc., Cary, NC)

Results

Factors related to ureteral stenting

Among 56 patients (14 seminoma and 42 non-seminoma) treated for metastasis of testicular tumors, ureteral stenting was performed on 12 patients before chemotherapy. As shown in Table 1, the proportion of patients with ureteral stenting was significantly higher in seminoma than in non-seminoma (47% and 12%, respectively, $P<0.05$). As for risk classification, all seven seminoma patients were classified as having a good prognosis according to the International Germ Cell Consensus Classification Group (IGCCCG) criteria (14), whereas four of five non-seminoma patients (80%) were classified into the intermediate or poor prognosis group. The median RPLN size of 12 patients was significantly greater than that of 31 patients having RPLN metastases and

treated without ureteral stenting (8.4 cm and 4.0cm, respectively: P<0.05).There was no significant difference in age or IGCCCG category distribution.

Clinical course for ureteral obstruction

There were no episodes of stent failure such as worsening hydronephrosis or inability to replace stent during stent replacement procedure. One patient developed the definite upper urinary tract infection, which could be managed with broad-spectrum antibiotics. During chemotherapy, two complications directly related to ureteral stent were observed. One was intraureteral migration, which needed ureteroscopy for removal. Another was fistula formation between ureter and necrotized lymph node mass. In the case, partial ureterectomy was performed in combined with RPLND.

In all seven seminoma patients, the ureteral stent was removed after chemotherapy (Table 2). The ureteral stent was removed after induction chemotherapy in six patients, and after salvage chemotherapy in the remaining seminoma patient. In contrast, the ureteral stent could not be removed after chemotherapy in non-seminoma patients. However, the ureteral stent was removed after RPLND in four of five non-seminoma patients. The remaining non-seminoma patient died of cancer without marker normalization and without removal of the ureteral stent.

During RPLND, the ureter was spared in three patients, and partial ureterectomy was needed in one patient, who had developed a fistula between the ureter and a necrotized lymph node mass during chemotherapy. There were no cases needing adjunctive nephrectomy at RPLND. As for the pathological findings at RPLND, no residual germ cell cancer or teratoma element was identified in three patients, and a few foci of adenocarcinoma in a residual teratoma were identified in a patient who underwent RPLND with alpha fetoprotein (AFP)-positive status. In all four patients, no adjuvant chemotherapy was performed after RPLND. These 11 patients continued with no evidence of disease at a median follow-up of 44 months (range 6 to 97 months).

Change of renal functions during and after treatment

Ureteral stenting tended to increase the median eGFR from 68.3 ml/min to 82.5 ml/min, although the difference was not statistically significant (Figure 1). Importantly, three patients presented insufficient renal function for chemotherapy including cisplatin (less than 60 ml/min eGFR), and ureteral stenting improved eGFR to more than 60 ml/min in these three patients before chemotherapy. On the other hand, chemotherapy decreased eGFR significantly (P=0.016), and the

eGFR was below 60 ml/min in six of 11 patients after treatment. However, no further deterioration in eGFR was observed at one year after the last treatment.

To identify the factors related to deterioration of renal functions, we compared patient profiles, treatment procedures, and CT findings at the last follow-up of patients with eGFR above and below 60 ml/min after treatment (Table 3). The CT findings of the kidney at the last follow up were normal in all patients whose eGFR was above 60 ml/min. In contrast, persistent hydronephrosis or apparent kidney atrophy was observed in five of six patients whose eGFR was below 60 ml/min. There were no significant differences in age, histology, chemotherapy courses, and history of RPLND between each group.

Discussion

Once inserted, a ureteral stent or PCN usually becomes permanent in patients with advanced cancers other than testicular tumor because they are not curable (7-9). On the other hand, most advanced testicular tumors can be cured by chemotherapy and surgery. Therefore, sparing the involved kidney and preservation of renal function are important clinical goals. However, to our

knowledge, there has been no report focused on the outcome of ureteral stent management during chemotherapy for testicular tumor. In the present retrospective study, we showed that ureteral stenting effectively improved renal function, which allowed completion of chemotherapy with adequate drug intensity. Second, we showed that involved ureters can be spared in most cases without worsening the oncological outcome.

The incidences of hydronephrosis in advanced seminoma and non-seminoma were reported to be about 25% and 35%, respectively (4, 5). In our series, ureteral stenting was needed in 21% of advanced testicular tumor patients, especially in the patients with a larger RPLN mass (median diameter of 8.4 cm). The proportion of ureteral stenting in seminoma was 45% in our series, and higher than previous reports (4). This might be a result of selection bias since most seminoma patients were initially diagnosed at community hospitals and referred to our hospital for treatment of advanced disease.

In the present study, all seminoma patients were cured by chemotherapy, and the stent could be removed in all cases after chemotherapy alone. In contrast, all non-seminoma patients underwent RPLND after chemotherapy, except one patient who died of the disease during chemotherapy. At RPLND, the

involved ureter was spared in three patients, and partial ureterectomy was needed in the remaining one. The ureteral stent could be removed in all patients after RPLND. It is important to estimate the risk of residual viable cancer around the involved ureter and to decide whether involved ureters can be spared or resected adjunctively at RPLND. Nash et al. reported that en block nephrectomy was performed at RPLND in 19% of post-chemotherapy non-seminoma patients (15). Stephenson et al. reported that adjunctive nephrectomy was necessary in 53% of non-seminoma patients with risk factors for residual viable cancer. The proposed risk factors for adjunctive nephrectomy include post-salvage chemotherapy, desperation RPLND, late relapse, and reoperative RPLND (16). In the present study, pathological examination of RPLND specimens revealed only necrotic tissue in three of four patients. The other patient, who underwent desperation RPLND with elevated AFP, had a teratoma with malignant transformation, but the surgical margin was negative. There was no recurrence after RPLND in all patients. We consider kidney-sparing surgery possible in selected cases with attention to the surgical margin.

The primary purpose of ureteral stenting is safe delivery of chemotherapy and preservation of renal function during chemotherapy. In our data, ureteral

stenting improved eGFR to more than 60 ml/min in all patients. As a result, induction chemotherapy was possible without dose reduction in 90% of treatment courses. The drug intensity of the induction chemotherapy was similar to that of our previous study (17). However, eGFR decreased significantly to below 60 ml/min in six of 11 patients after chemotherapy even if ureteral obstruction was treated with ureteral stenting.

Previous studies have demonstrated a 20–30% reduction in the GFR in long-term follow up after chemotherapy for testicular tumor (18). Age at treatment and the type of treatment were associated with renal impairment (2). We previously reported that patients who developed renal impairment during chemotherapy might be at risk of further elevation of serum creatinine during long-term follow up (19). In the present series, the follow-up CT revealed progressive renal atrophy in three cases and persistent mild hydronephrosis in three cases in the patients whose eGFR fell below 60 ml/min. The patient age, histological type, number of courses of chemotherapy, and undergoing of RPLND were not associated with eGFR after chemotherapy. The severity of hydronephrosis might be associated with the renal impairment, but we could not adequately grade hydronephrosis in the present retrospective study.

Testicular tumor is highly curable cancer; therefore, assessment of the long-term morbidity is important due to the life expectancy of this group of young men (3). The morbidity includes secondary malignant neoplasms, neuropathy, gonadal dysfunction, nephrotoxicity, and cardiovascular disease. The latter two morbidities may be associated because a large population-based study showed a graded association between a reduced eGFR and the risk of cardiovascular events (20). To avoid post-treatment eGFR reduction, it is a reasonable to treat advanced testicular tumor patients with the intention of sparing the kidneys when possible.

In conclusion, Ureteral obstruction due to testicular tumor was relieved after chemotherapy or RPLND in most of cases. Ureteral stenting was effective to improve renal function before chemotherapy, although we should pay special attention to deterioration of renal function during or after chemotherapy.

Figure legend

Figure 1　Changes in eGFR in each patient

The eGFR during treatment of each patient who needed ureteral stenting is plotted. The treatment for seminoma patients was chemotherapy. For non-seminoma patients, treatment was chemotherapy and RPLND. Note that a significant decrease in eGFR was observed after treatment despite ureteral stenting.

References

1. Hansen SW, Groth S, Daugaard G, Rossing N, Rorth M. Long-term effect on renal function and blood pressure of treatment with cisplatin, vinblastine, and bleomycin in patients with germ cell cancer. J Clin Oncol 1988 6(11):1728-31.

2. Fossa SD, Aass N, Winderen M, Bormer OP, Olsen DR. Long-term renal function after treatment for malignant germ-cell tumor. Ann Oncol 2002 13(2):222-8.

3. Travis LB, Beard C, Allan JM, Dahl AA, Feldman DR, Oldenburg J, et al. Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 2010 102(15):1114-30.

4. Babaian RJ and Zagars GK. Testicular seminoma: The M.D. Anderson experience. An analysis of pathological and patient characteristics, and treatment recommendations. J Urol 1988 139(2):311-4.

5. Barton C, Duchesne G, Williams M, Fisher C, Horwich A. The impact of hydronephrosis on renal function in patients treated with cisplatin-based chemotherapy for metastatic nonseminomatous germ cell tumors. Cancer 1988 62(7):1439-43.

6. Richie JP. Diagnosis and staging of testicular tumors. In Skinner DG,

Lieskovsky G eds, Diagnosis and management of genitourinary cancer. 1st edn, Chapt 32. Philadelphia: Saunders, 1988: 498-607.

7. Ganatra AM, Loughlin KR. The management of malignant ureteral obstruction treated with ureteral stents. J Urol 2005 174(6):2125-88.

8. Rose PG, Ali S, Whitney CW, Lanciano R, Stehman FB. Impact of hydronephrosis on outcome of stage IIIB cervical cancer patients with disease limited to the pelvis, treated with radiation and concurrent chemotherapy: a Gynecologic Oncology Group study. Gynecol Oncol 2010 117(2):270-5.

9. Kouba E, Wallen EM, Pruthi RS. Management of ureteral obstruction due to advanced malignancy: optimizing therapeutic and palliative outcomes. J Urol 2008 180(2):444-50.

10. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987 316(23):1435-1440.

11. Motzer RJ, Sheinfeld J, Mazumdar M, Bains M, Mariani T, Bacik J, et al. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 2000 18(12):2413-8.

12. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Collaborators

developing the Japanese equation for estimated GFR Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009 53(6):982-92.

13. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003 41(1):1-12.

14. International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: A prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997 15(2):594-603.

15. Nash PA, Leibovitch I, Foster RS, Bihrle R, Rowland RG, Donohue JP. En bloc nephrectomy in patients undergoing post-chemotherapy retroperitoneal lymph node dissection for nonseminomatous testis cancer: indication, implication and outcomes. J Urol 1998 159(3):707-710.

16. Stephenson AJ, Tal R, Sheinfeld J. Adjunctive nephrectomy at post-chemotherapy retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer. J Urol 2006 176(5):1996-9.

17. Kawai K, Ando S, Hinotsu S, Oikawa T, Sekido N, Miyanaga N, et al.

Completion and toxicity of induction chemotherapy for metastatic testicular cancer: an updated evaluation of Japanese patients. Jpn J Clin Oncol 2006 36(7):425-31.

18. Hartmann JT, Kollmannsberger C, Kanz L, Bokemeyer C. Platinum organ toxicity and possible prevention in patients with testicular cancer. Int J Cancer 1999 83(6):866-9.

19. Hisamatsu E, Kawai K, Hinotsu S, Miyanaga N, Shimazui T, Akaza H. Serum creatinine and cholesterol levels of testicular cancer patients in long-term follow up. Int J Urol 2005 12(8):751-6.

20. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004 351(13):1296-305.

Table 1 Patient Characteristics

	Without stent placement (N=44)	With stent placement (N=12)
Age	32 (17-65)*	39 (26-58)*
Histology (S/NS)	8/36#	7/5#
IGCCCG category (G/I/P)	16/9/19	8/2/2
Size of RP mass(cm)	4.0 (1-15.0)*,**,#	8.4 (4.5-20.0)*,#
Stent placement	none	12
Left /Right/Bilateral		7/4/1
Chemotherapy		
Induction	20	6
Induction + salvage	24	6

S: seminoma, NS: non-seminoma
G: good risk, I: intermediate risk, P: poor risk
RP: retroperitoneal
*Mean (range), **N=31
#P<0.05

Table 2 Treatment Outcome

	Seminoma (N=7)	Non-seminoma (N=5)
Marker normalization	7	4
RPLND	0	4
Pathology	-	necrosis 3 teratoma with MT 1
Stent removal	7	4
Outcome	NED 7	NED 4 DOD 1

RPLND: retroperitoneal lymph node dissection
MT: malignant transformation, NED: no evidence of disease
DOD: Died of disease

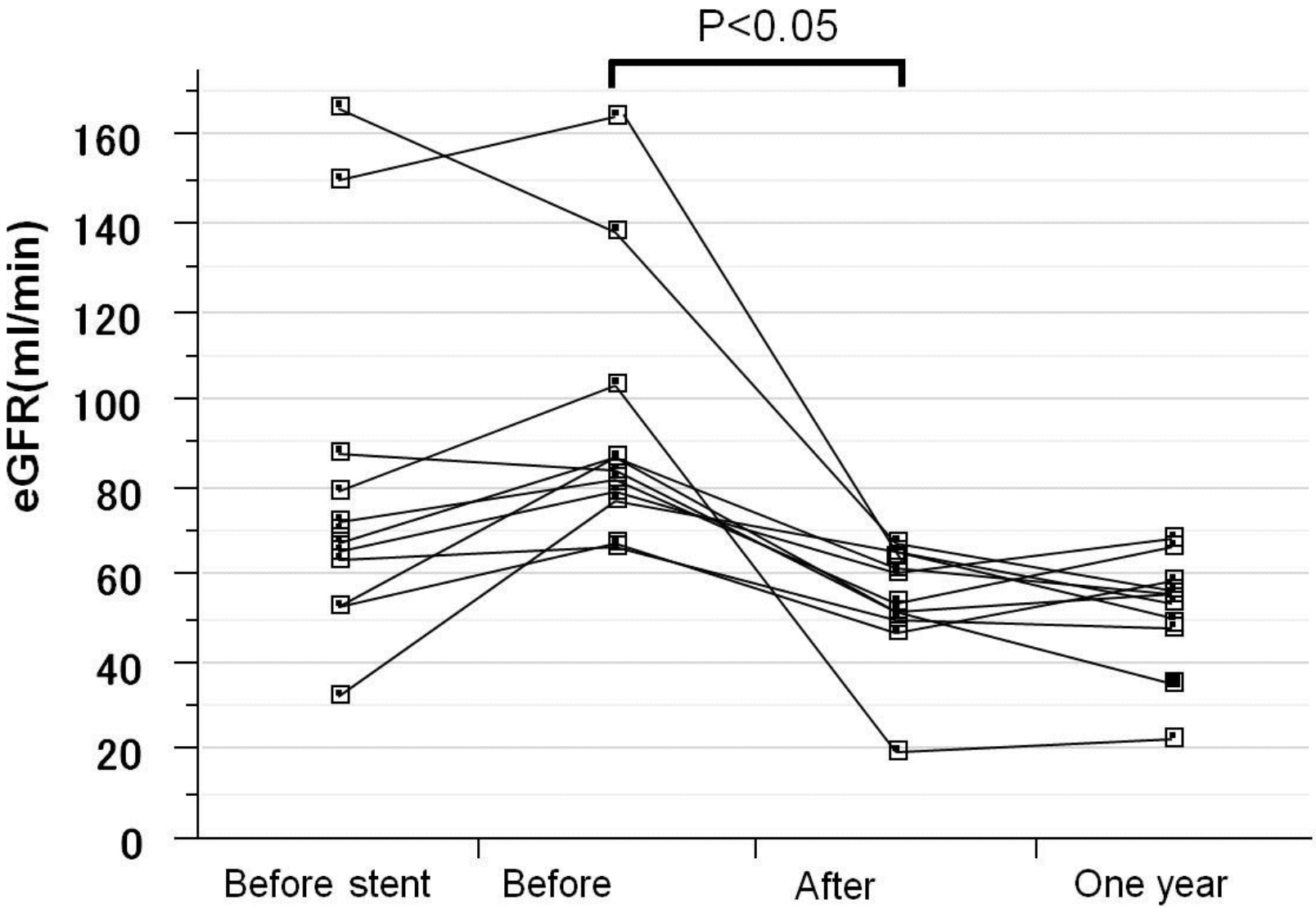
Table 3
Clinical parameters and eGFR at completion of treatment

	eGFR≥60ml/min (N=5)	eGFR<60ml/min (N=6)
Age*	38	42
Histology		
Seminoma	3	4
Non-seminoma	2	2
Cycles of chemotherapy		
≤ 4 cycles	2	4
≥ 5 cycles	3	2
RPLND	2	2
CT findings at last follow up**	normal: 5[#]	normal: 1[#] hydronephrosis: 3[##] atrophic kidney: 3[##]

*Median , ** Median 33 months, [#] P<0.05

[##]One patient showed hydronephrosis and atrophy

Figure 1


P<0.05
eGFR(ml/min)
160
140
120
100
80
60
40
20
0
Before stent
Before
After
One year