Clinical factor affecting the recovery of kidney function in clinically localized renal cell carcinoma patients who underwent nephron-sparing surgery.

Takahiro Osawa[a,b], Hiroshi Harada[c], Koji Oba[d], Toshimori Seki[a], Masaki Togashi[a]

a. Department of Urology, Sapporo City General Hospital, Sapporo, 060-8604, Japan

b. Department of Urology, Graduate School of Medicine, Hokkaido University, Sapporo, 060-8604, Japan

c. Department of Kidney Transplantation, Sapporo City General Hospital, Sapporo, 060-8604, Japan

d. Translational Research and Clinical Trial Center, Hokkaido University Hospital, Sapporo, 060-8604, Japan

Running title: kidney function after nephron-sparing surgery

Keywords: renal cell carcinoma; nephron-sparing surgery; renal function; chronic kidney disease; diabetes mellitus

Address correspondence to: Takahiro Osawa,

Department of Urology, Sapporo City General Hospital, Sapporo, Hokkaido, Japan

North-11, West-13, Chuo-ku, Sapporo, 060-8604, Japan

Tel: +81-11-726-2211 Fax: +81-11-726-7912 E-mail: taka0573@gmail.com

Abstract

Introduction

Nephron-sparing surgery (NSS) has become the standard treatment for small renal cell carcinoma because of its comparable oncological outcome and superior patient survival compared to total nephrectomy. However, the precise chronological course of recovery from initial kidney damage and the factors responsible for it remain unknown.

Materials and Methods

Seventy-one patients who underwent NSS were enrolled. To elucidate the chronological changes in kidney function that occur after NSS, the estimated glomerular filtration rate (eGFR) was calculated at different two points, the early (7 days after surgery) and late time points (more than 12 months after surgery), and compared with the preoperative eGFR. Perioperative factors were applied to a multivariate regression model to investigate the factors that most affect patient recovery from nephron damage.

Results

eGFR was decreased at the early time point but had partially recovered at the late time point. Male gender, ischemic time, and tumor size were found to be significant predictors of the initial drop in eGFR. The only significant factor that prevented later functional recovery was the presence of DM.

Conclusion

Several perioperative factors significantly influence early kidney damage; however, the presence of

DM is the only factor affecting the risk of long-term chronic kidney damage.

Introduction

The overall incidence of renal cell carcinoma has increased steadily during the past decade. The majority of incidentally detected renal cortical tumors are small. Tumors of less than 4 cm in diameter (pathological T1a) currently account for the largest proportion of renal cell carcinomas [1]. Several investigators have reported that, for most patients diagnosed with this stage disease, nephron sparing surgery (NSS) is superior to radical nephrectomy with regard to the overall postoperative kidney function achieved [2]. In addition, for small renal tumors NSS achieves equivalent oncological outcomes to radical nephrectomy [3,4]. Therefore, NSS is the gold standard for small renal cortical tumors due to its effects on long-term kidney function and oncological outcomes.

Meanwhile, progressively worsening chronic kidney disease (CKD) is associated with an increased risk of cardiovascular events, hospitalization, and death among the general population in Western countries [5]. Recent reports from Japan have also confirmed that chronic kidney disease is a significant risk for cardiovascular disease (CVD) events and all-cause mortality, suggesting that chronic kidney disease represents a major public health issue that is independent of ethnicity [6].

Recently, several studies have attempted to investigate the long-term outcomes after NSS with regard to postoperative kidney function according to the estimated glomerular filtration rate (eGFR), which defines kidney function more accurately [7]. However, the precise chronological course of recovery from the initial kidney damage and factors that most affect recovery from initial kidney damage remain unclear. Thus, we conducted a retrospective study to solve these problems.

The goal of this study is to elucidate the time course of kidney function after NSS and to identify which variables including patient characteristics and surgical factors influence postoperative functional recovery of the kidneys.

Patients and Methods

We performed a hospital-based retrospective cohort study analyzing kidney function data from patients who underwent NSS at Sapporo City General Hospital. Seventy-one patients who underwent NSS from February 2001 to April 2008 were enrolled. Of these, 26 received open NSS, and the other 45 received laparoscopic NSS. Patients with radiological evidence of metastatic disease, multiple tumors, or solitary kidney were excluded from the study. Our primary outcome was the change in eGFR between the baseline and the early or late postoperative time point because eGFR is a low-cost noninvasive method of evaluating kidney function.

Serum creatinine was measured preoperatively and at postoperative outpatient follow-up examinations in all patients, and eGFR was calculated using the estimation equation for Japanese patients with CKD ($eGFR=175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female)), which was developed by the Japanese Society of Nephrology [8,9]. The eGFR at the early (7 days postoperatively) and late time points (more than 12 months after surgery, mean: 40.0 (12 - 92) months postoperatively) were compared with the preoperative measurements. In order to study the long-term recovery of kidney function from perioperative kidney damage, we included 54 patients who had been followed-up for more than 12 months for analyzing renal function at the late point.

A preoperative evaluation of medical history including co-morbidities was performed using the patients' medical records. As possible predictors of kidney function at both the early and late postoperative time points, information about age, gender, pertinent comorbidities (hypertension, diabetes mellitus, DM, and CKD), operative approach (open NSS or laparoscopic NSS), operative time, ischemic time (transient artery and vein occlusion using ice slush), and tumor size were collected. Intraoperative information, including the operation time, ischemic time, and operative approach, was obtained from the patients' anesthesia records. Tumor size was recorded as the longest dimension of the tumor in the excised specimen. Patients with DM were defined as those who met the relevant diagnostic criteria of type 2 DM and required glycemic control. Baseline chronic kidney disease was defined as a kidney function of less than 60 ml/min/1.73m^2 (CKD stage 3 or 4).

Mean (median, range) and percentage values were used to describe the background characteristics of the study population. Comparisons of eGFR among the three time points were performed using mixed effect model to account for within-subject correlation. In the mixed effect model, unstructured form was used for the within-subject variance covariance matrix. Multiple linear regression analysis was used to identify the independent predictors of kidney function at the early and late postoperative time points. The JMP software (SAS Institute, Cary, NC) and SAS (SAS Institute, Cary, NC) was used for statistical analyses, and *p* values of <0.05 were judged to be statistically significant.

Results

The characteristics of the 71 patients that underwent NSS for renal tumors are listed in Table 1. Among them, 26 and 45 patients underwent open and laparoscopic (including hand-assisted surgery) NSS, respectively. The mean age of the patients was 58.5-years-old (range, from 30 to 84-years-old). Fifty-three were male and 18 were female. The mean operative time and ischemic time were 237.3 min and 45.1 min, respectively. The patients' operative parameters and pathological diagnoses are listed in Table 2.

We evaluated the effect of NSS on the recovery of kidney function at the three time points. At the late time point, the mean eGFR was significantly decreased compared to the preoperative value ($p < 0.05$), although it was evident that there was a trend toward progressive recovery after an initial drop in eGFR at the early time point (Fig. 1). The results obtained by regression analysis are summarized as the coefficients of the statistically significant predictors of kidney function at the early (Table 3) and late time points (Table 4).

We found that male gender (OR=-9.3; 95% CI, -18 to -0.50; $p = 0.04$), longer ischemic time (OR=-0.17; 95% CI, -0.32 to -0.03; $p = 0.02$), and tumor size (OR=-0.42; 95% CI, -0.79 to -0.05; $p = 0.03$) were significantly associated with decreased kidney function at the early time point. ischemic time was the most important factor governing kidney function loss at the early time point. Larger tumor resection during NSS resulted in greater nephron loss and a reduction in postoperative kidney function. Each millimeter increase in tumor size led to a 0.4% decrease in kidney function at the early time point after surgery.

Indeed, among 7 patients with DM, 4 (57.1%) developed CKD during the subsequent follow-up in our study. Interestingly, different from the factors associated with early kidney function recovery, DM remained as the sole significant predictor of kidney function over the long term and was correlated with decreased kidney function (OR=-15; 95% CI, -25 to -5.4, p = 0.01). Furthermore, patients with DM showed significant renal function loss compared with patients without DM during follow-up period. The interaction between time and DM was statistically significant in the mixed effect model (p = 0.010, Fig.2). None of the other patient-specific or surgical factors affected long-term kidney function. No patient in the cohort required dialysis during the postoperative follow-up.

Discussion

In contrast to radical nephrectomy, NSS is associated with a decreased risk of CKD, a lower subsequent CVD risk, improved patient prognosis, and comparable oncological outcome [2-4]. These findings all support the increased use of NSS for the treatment of small renal tumors. As a result, NSS is being increasingly used to treat renal cell carcinoma. NSS is especially indicated for patients with conditions that can lead to CKD such as hypertension and DM, etc. Although these clinical factors are thought to affect the magnitude of kidney function loss after NSS, the role of these factors in preventing kidney function recovery have not been well studied.

We found that there was a significant initial drop of eGFR in the operated kidney's contribution to overall function at the early time point, followed by a long-term recovery that never reached the preoperative mean eGFR (63.5ml/min1.73m^2 at the late point vs. 72.4ml/min1.73m^2 before surgery), resulting in a loss of mean contribution of 12.3%. This damage was probably caused by the resection of healthy renal parenchyma and secondary parenchymal damage, which was presumably caused by the warm ischemia and/or the loss of blood flow in the vicinity of the resected site. However, it is important to point out that, even though there is a documented loss of kidney function, this only lasts for a limited time and is incomplete, as demonstrated by the patients' progressive recovery. This suggests that some nephrons have the potential to recover. Therefore, longer follow-up is needed to discover whether the kidney is able to achieve a full recovery over time. Other groups have also noted this observation [10,11].

We found that ischemic time was independently associated with a decline in kidney function at the early time point. As reported previously, the duration of ischemic time is a strong modifiable surgical risk factor for decreased kidney function after NSS [10]. For larger or infiltrating tumors, transient clamping of the renal vessels is necessary to decrease blood loss and achieve a bloodless surgical field. To avoid damaging kidney function during warm ischemia, surgeons should complete the tumor excision within about 30 minutes [12]. Renal hypothermia not only protects against post-ischemic renal injury, but also allows for a longer ischemic time. We use ice slush during the temporary clamping of the renal vessels to reduce the possibility of injuries to the kidney. In our series, the ischemic time was longer in the laparoscopic surgery group than in open surgery group (precise data not shown), although the operative procedure was not a significant predictor of worsening postoperative kidney function. Laparoscopic NSS has emerged as a minimally invasive extirpative approach to NSS [13]. Although this technique has some advantages compared to open NSS, including less blood loss, reduced postoperative analgesics use, shorter hospital stay, and faster recuperation, the effects of its longer ischemic time remain a problem. We need to make further efforts to limit the ischemic time and kidney damage inflicted during NSS.

We found that tumor size was a significant predictor of decreased kidney function after NSS. Some investigators have prospectively evaluated the volume of kidney tissue resected after NSS and calculated the GFR of the affected kidney from postoperative renal scans. In these studies, the reduction in GFR and resected kidney volume were similar, and renal volume reduction was the most significant independent predictor of GFR reduction [10,14]. Gender was also shown to be a predictor of kidney functional decline in our series. Other groups have also noted this observation [7,10].

A past medical history of DM was found to be independently associated with a decline in kidney function only at the late time point. DM has also been found to be a risk factor for CKD development after NSS in previous reports [15]. Our study showed that 4 out of 7 (57.1%) patients with DM displayed decreased kidney function after surgery. In particular, type 2 diabetes is the leading cause of end-stage renal disease not only in the Western world but also in Japan [16,17]. Many, but not all, patients with type 2 diabetes develop renal dysfunction during their lifetime. Prospective clinical trials have demonstrated that improvements in glycemic control, particularly early in treatment, are associated with reductions in the incidence of microvascular complications, including CKD [18]. Even after successful surgery, it is recommended that these patients should achieve appropriate glycemic control to inhibit further renal deterioration.

This study had several limitations. First, the data were collected in a retrospective fashion, and we were unable to collect potential known and unknown confounders. In addition, information about the precise location of renal tumors (e.g., endophytic, mesophytic, exophytic) and estimates of the reduction in kidney volume were not obtained. In particular, kidney volume reduction has been shown to be a major predictor of the extent of kidney function decline after NSS [14,19]. Furthermore, eGFR might not be sufficiently sensitive to detect significant changes in postoperative kidney function, particularly in the context of a normally functioning contralateral kidney [11]. A prospective study involving a larger sample size, longer follow-up period, and the use of the most accurate method for estimating GFR is necessary.

Conclusions

The results of our study showed that perioperative factors such as male gender, ischemic time, and tumor size significantly influence kidney damage early after NSS. However, only the presence of DM, which is independent of surgery-related factors, affects the risk of long-term chronic kidney damage after NSS. Long-term follow-up is necessary, especially for patients who display this risk factor, even after successful NSS.

References

1 Nguyen MM, Gill IS, Ellison LM; The evolving presentation of renal carcinoma in the united states: Trends from the surveillance, epidemiology, and end results program. J Urol 2006; **176**: 2397-2400; discussion 2400.

2 Huang WC, Elkin EB, Levey AS, Jang TL, Russo P; Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? J Urol 2009; **181**: 55-61; discussion 61-52.

3 Belldegrun A, Tsui KH, deKernion JB, Smith RB; Efficacy of nephron-sparing surgery for renal cell carcinoma: Analysis based on the new 1997 tumor-node-metastasis staging system. J Clin Oncol 1999; **17**: 2868-2875.

4 Herr HW; Partial nephrectomy for unilateral renal carcinoma and a normal contralateral kidney: 10-year followup. J Urol 1999; **161**: 33-34; discussion 34-35.

5 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**: 1296-1305.

6 Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M; Chronic kidney disease and cardiovascular disease in a general japanese population: The hisayama study. Kidney Int 2005; **68**: 228-236.

7 Clark MA, Shikanov S, Raman JD, Smith B, Kaag M, Russo P, Wheat JC, Wolf JS, Jr., Matin SF, Huang WC, Shalhav AL, Eggener SE; Chronic kidney disease before and after partial nephrectomy. J Urol 2011; **185**: 43-48.

8 Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S; Modification of the modification of diet in renal disease (mdrd) study equation for japan. Am J Kidney Dis 2007; **50**: 927-937.

9 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Revised equations for estimated gfr from serum creatinine in japan. Am J Kidney Dis 2009; **53**: 982-992.

10 Lane BR, Novick AC, Babineau D, Fergany AF, Kaouk JH, Gill IS; Comparison of laparoscopic and open partial nephrectomy for tumor in a solitary kidney. J Urol 2008; **179**: 847-851; discussion 852.

11 Porpiglia F, Renard J, Billia M, Musso F, Volpe A, Burruni R, Terrone C, Colla L, Piccoli G, Podio V, Scarpa RM; Is renal warm ischemia over 30 minutes during laparoscopic partial nephrectomy possible? One-year results of a prospective study. Eur Urol 2007; **52**: 1170-1178.

12 Novick AC; Renal hypothermia: In vivo and ex vivo. Urol Clin North Am 1983; **10**: 637-644.

13 Gill IS, Kavoussi LR, Lane BR, Blute ML, Babineau D, Colombo JR, Jr., Frank I, Permpongkosol S, Weight CJ, Kaouk JH, Kattan MW, Novick AC; Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007; **178**: 41-46.

14 Song C, Bang JK, Park HK, Ahn H; Factors influencing renal function reduction after partial nephrectomy. J Urol 2009; **181**: 48-53; discussion 53-44.

15 Jeon HG, Jeong IG, Lee JW, Lee SE, Lee E; Prognostic factors for chronic kidney disease after curative surgery in patients with small renal tumors. Urology 2009; **74**: 1064-1068.

16 Ritz E, Orth SR; Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999; **341**: 1127-1133.

17 Wakai K, Nakai S, Kikuchi K, Iseki K, Miwa N, Masakane I, Wada A, Shinzato T, Nagura Y, Akiba T; Trends in incidence of end-stage renal disease in japan, 1983-2000: Age-adjusted and age-specific rates by gender and cause. Nephrol Dial Transplant 2004; **19**: 2044-2052.

18 Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH, Jr., Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I; Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: An analysis of the accord randomised trial. Lancet 2010; **376**: 419-430.

19 Chan AA, Wood CG, Caicedo J, Munsell MF, Matin SF; Predictors of unilateral renal function after open and laparoscopic partial nephrectomy. Urology 2010; **75**: 295-302.

Table 1 Patients' demographic data

No. of pts	71
Mean age, yr (range)	58.5 (30-84)
Male gender	53 (74.6%)
Mean BMI, kg/m^2 (range)	24.14 (16.9-34.6)
Left-sided tumor (no. of pts)	35 (49.0%)
Mean tumor size, mm (range)	23.0 (9-64)
History of hypertension (no. of pts)	20 (28.2%)
History of diabetes (no. of pts)	7 (10.0%)
Mean preoperative eGFR ($ml/min/1.73m^2$)	72.3 (45.5-96.7)
CKD stage 3	10 (14.1%)

Pts: patients

Table 2 Operative parameters and pathological diagnosis

Retroperitoneal approach (no. of pts)	66 (93.0%)
Laparoscopic NSS (no. of pts)	45 (63.4%)
Mean operative time, min (median; range)	237.3 (240; 115-415)
Mean ischemic time, min (median; range)	45.1 (35; 13-144)
Histological classification (no. of pts (%))	
Clear cell carcinoma (T1a)	64 (90.1%)
Angiomyolipoma	7 (9.9%)

Pts: patients

Table 3 Results of the multiple regression analysis of factors affecting kidney function at the early time point

Variable	Model coefficient (95% CI)	p-value
Patient factors		
Age	-0.11 (-0.42, 0.19)	0.46
Male gender	**-9.25 (-18.00, -0.50)**	**0.04**
Hypertension	-6.66 (-14.98, 1.66)	0.11
Diabetes	-6.79 (-18.51, 4.93)	0.25
Baseline CKD	-1.36 (-11.90, 9.18)	0.80
Surgical factors		
Operative approach (Open technique)	6.68 (-3.20, 16.55)	0.18
Operative time (min)	-0.02 (-0.09, 0.06)	0.67
Ischemic time (min)	**-0.17 (-0.32, -0.03)**	**0.02**
Tumor size (mm)	**-0.42 (-0.79, -0.05)**	**0.03**

Statistically significant differences are depicted in bold font ($P < 0.05$)

Table 4 Results of the multiple regression analysis of factors affecting kidney function at the late time point

Variable	Model coefficient (95% CI)	p-value
Patient factors		
Age	-0.18 (-0.47, 0.11)	0.23
Male gender	0.29 (-7.75, 8.33)	0.94
Hypertension	-2.96 (-9.79, 3.88)	0.39
Diabetes	**-15.13 (-24.82, -5.44)**	**<0.01**
Baseline CKD	-4.33 (-13.00, 4.34)	0.32
Surgical factors		
Operative approach (Open technique)	4.23 (-4.05, 12.51)	0.31
Operative time (min)	0.01 (-0.05, 0.07)	0.72
Ischemic time (min)	-0.02 (-0.15, 0.12)	0.79
Tumor size (mm)	-0.11 (-0.48, 0.25)	0.54

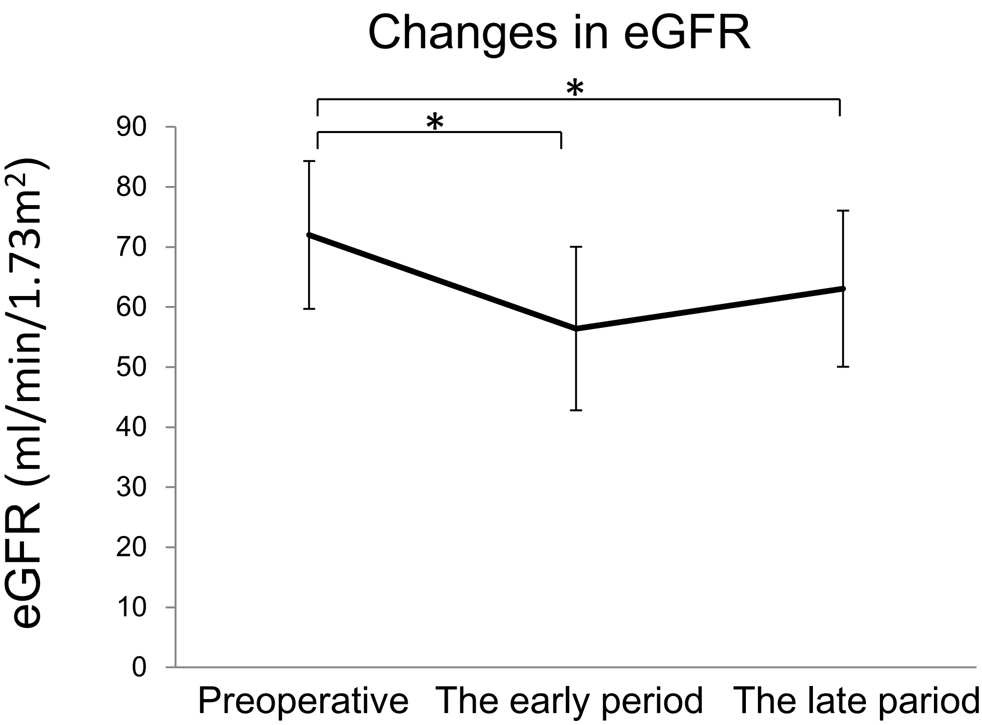
Statistically significant differences are depicted in bold font ($P < 0.05$)

Figure legends

Figure1. Changes in eGFR between pre- and post- nephron sparing surgery. At the late time point, the eGFR was significantly decreased compared to the preoperative value, although it was evident that there was a trend toward a progressive recovery after an initial drop in eGFR at the early time point. Error bars indicate standard deviation. * $p<0.05$ vs. preoperative eGFR.

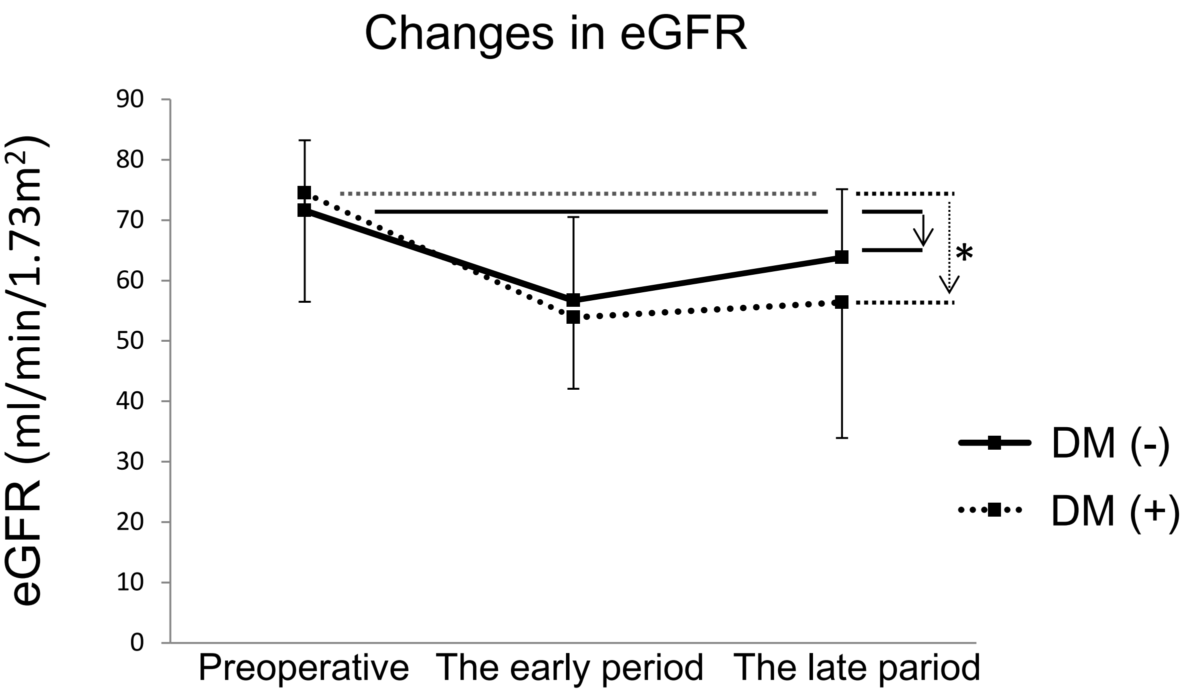
Figure 2 Changes in eGFR between patints with/without DM. Patients diagnosed as DM showed poor renal function recovery after NSS. Patients with DM showed significant renal function loss (% of decrease from preoperative eGFR) compared with patients without DM. Error bars indicate standard deviation. (* $p<0.05$)

Figure 1



Mean eGFR (range)	72.4 (45.5-96.7)	57.7 (31.1-90.7)	63.5 (24.7-93.3)

Figure 2



	Preoperative	The early period	The late pariod
Mean eGFR DM(+)	74.5	53.9	58.5
Mean eGFR DM(-)	71.6	56.7	64.1