PARTIAL NEPHRECTOMY FOR SMALL LOCALIZED RENAL CELL CARCINOMA

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We retrospectively reviewed the records of 54 patients with RCC who underwent partial nephrectomy for the primary lesion between 1992 and 2001. The indications for partial nephrectomy were elective in 43 and imperative in 11 patients. We selected 51 patients with clinical stage T1a who underwent open radical nephrectomy for localized RCC for comparison during the same period. We evaluated the peri- and postoperative complications, disease-free survival rates and changes of renal function in the partial nephrectomy (PN) group, compared to the radical nephrectomy (RN) group. There was no significant difference with regard to pathological findings and clinical outcomes between two groups, except for the amount of intraoperative bleeding. Three patients in the PN group developed postoperative complications, consisting of urine leakage in 2 patients and renal hypertension in 1 patient. The 5-year disease-free survival rates in the PN and RN groups were 90% and 97%, respectively. Local recurrence from the resected area of the renal parenchyma was not found in patients in the PN group. All patients in the PN group maintained satisfactory and stable renal function. In the RN group, renal function slowly deteriorated in 2 patients. Therefore, partial nephrectomy offers cancer control and an acceptable low mortality rate, comparable to those of radical nephrectomy.

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Key words : Renal cell carcinoma, Partial nephrectomy

INTRODUCTION

Partial nephrectomy has been performed on patients with renal cell carcinoma (RCC) who have a solitary kidney, bilateral tumors and compromised contralateral kidney. In recent years the number of incidentally detected tumors has been increasing owing to easily available examinations for health care and the recent development of radiological imaging techniques. Since incidentally detected tumors tend to be smaller in size and earlier in clinical stage, they are typically amenable to partial nephrectomy, and the indications for this operation for RCC have been expanded into the setting of a normal contralateral kidney. Many investigators recently reported favorable results of partial nephrectomy in imperative cases as well as in elective cases[1–6] However, there is still controversy as to whether partial nephrectomy should be the standard procedure of choice given a normal contralateral kidney[7,8].

The purpose to perform partial nephrectomy is to achieve maximal cancer control and to preserve adequate renal function. Therefore, the outcome must be equivalent to radical nephrectomy with low morbidity and mortality. In this study, we evaluated the clinical outcomes and renal function of patients who received partial nephrectomy, in comparison with those who received radical nephrectomy.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 54 patients with sporadic RCC who received partial nephrectomy between 1992 and 2001 at Sapporo Medical University Hospital. The indication for partial nephrectomy was elective in 43 patients. These patients were primarily selected on the basis of a tumor size of 4 cm or less and a peripherally located tumor without extension toward the hilum. The imperative indication was applicable to 3 patients with a solitary functional kidney (severely compromised renal function), 5 with bilateral asynchronous tumors and 3 with bilateral synchronous ones. We selected 51 patients with clinical stage T1a tumors who underwent open radical nephrectomy for localized RCC between 1990 and 2000 for comparison. The treatment modality chosen for an individual was based on the contralateral renal function, the patient's medical condition, the location of the tumor and the patient's preference.

The clinical characteristics of patients in the partial nephrectomy (PN) and radical nephrectomy (RN) groups are summarized in Table 1. There were no significant differences between the two groups with regard to sex, age, preoperative serum creatinine level and preoperative co-morbidity, including diabetes and hypertension, except for the duration of follow-up. Median followup was 44 months in the PN

Table 1. Clinical characteristics of patients treated with partial nephrectomy and radical nephrectomy

	Partial nephrectomy (n=54)	Radical nephrectomy (n=51)	P-value
Age. mean years (range)	57.3 (29–77)	57.9 (24–78)	NS*
No. of male/female	36/18	37/14	NS**
Followup: median months (range)	44 (11–108)	54 (10–127)	P=0.04*
No. of incidental tumors (%)	48 (88.9)	43 (84.3)	NS**
No. with co-morbidity (%)			NS**
Hypertension	20 (37.0)	16 (31.3)	
Diabetes	9 (16.7)	8 (15.9)	
24 h Ccr rate before surgery mean l/day±SD	124.4±38	116.0±34	NS*
Serum Cr level before surgery mean mg/dl±SD	0.8±0.27	0.8±0.20	NS*
No. with proteinuiria before surgery	4 (7.4)	6 (11.7)	NS**

* Using the Mann-Whitney U-test. ** Using χ^2 test. NS: Not significant.

group, and 54 months in the RN group. The primary lesion was incidentally discovered in most patients in both groups. The mean sizes of the tumors on computed tomography (CT) were 32 and 34 mm in the PN and RN groups, respectively, without a significant difference.

Pre- and post-operative examination

All patients underwent preoperative evaluation of medical history, physical examination, urinalysis and hematological screening. The preoperative radiologic examinations consisted of abdominal CT or ultrasound for the primary lesion in all patients, and chest CT or X-ray, and bone scintigraphy for distant metastasis. The primary tumor in all cases was clinically localized to kidney. No imaging studies revealed enlarged regional lymph nodes or abnormal findings for other organs in any patient. Proteinuria was defined as a positive reaction by dipstick.

The serum creatinine level was measured before surgery and 2 weeks after surgery in all patients. The creatinine clearance of 24-hour urine collection (24 h Ccr) both before and 2 weeks after nephrectomy was available for 40, 23 patients in the PN, RN group, respectively. In the 17 early patients of the PN group, including 2 imperative and 13 elective cases, we quantitatively evaluated the degree of impairment in the spared kidney by renography with ^{99m}Tc-mercaptacetyltriglycine (MAG-3) before surgery and 2 weeks, 3 months, 6 months after surgery. Split renal function was estimated as effective renal plasma flow (ERPF) of the kidney, defined as a formula: ERPF of the spared kidney/ERPF of the normal opposite kidney. After discharge, the serum creatinine level was measured periodically. In the RN group one patient who had been on dialysis due to chronic glomerulonephritis for 7 years was excluded from analysis of renal function. The primary lesion was pathologically staged based on the 5th modified TNM system according to the international Union Against Cancer[9].

Physical examination, renal and abdominal ultrasonography and chest CT were scheduled every 6 months in the 3 years after surgery and then every 12 months. Abdominal CT was an alternative to abdominal ultrasonography for some patients.

Surgical procedure

With regard to the surgical technique of partial nephrectomy, a flank extraperitoneal approach was usually performed. The entire renal surface except for the tumor area was dissected from the overlying fat tissue for detection of macroscopic satellite tumors. The renal artery and vein were temporarily occluded. Mannitol was administered routinely before vascular occlusion. Regional hypothermia was achieved by use of ice slush placed around the kidney for 15 minutes after vessel clamping. Vascular occlusion and parenchymal cooling ware performed in 50 of the 54 procedures. The tumor was removed en bloc with the perinephric fat lying on the surface of the tumor providing a 1 cm margin of normal renal tissue around the tumor. The surgical margin was confirmed to be cancer-free in frozen sections. When the collecting system was damaged, it was closed with interrupted or running absorbable sutures. Indigo carmine was routinely administered to verify that there was no leakage from the collecting system. Regional lymphadenectomy was not done in partial nephrectomy. Radical nephrectomy with regional lymphadenectomy was performed according to the standard procedure[10] The surgical approach was dependent on the location of the tumor. A thoracoabdominal and flank extraperitoneal approach was done in 40 and 11 patients, respectively.

Autologous blood was stocked preoperatively for 29 patients in the PN group and 7 in the RN group from 1995, but this has not done in the last 3 years.

Statistical analysis

Survival analysis was performed by the Kaplan-Meier method. The differences between the groups were determined by the log-rank test. The Mann-Whitney U-test and χ^2 test were used in analysis of differences between the PN and RN group, and paired tests in the analysis of difference for creatinine clearance level and serum creatinine level before and

after surgery.

RESULTS

Tables 2 and 3 summarize the pathological findings and operative outcomes for patients who underwent radical nephrectomy and partial nephrectomy.

Pathological findings

Pathological stage T3a was found in 4 patients in the PN group and in 2 in the RN group (Table 2). No significant difference was found between the 2 groups with regard to other pathological findings. No patients of the PN group were found to have a positive surgical margin in resected specimens.

Operative outcomes

There was no significant difference with respect to the operation time or the incidence of post-operative complications, except for the amount of intra-operative bleeding (Table 3). Although the amount of intraoperative bleeding was significantly larger in the PN group, the requirement for homologous transfusion was not significantly different between these two groups. Autologous transfusion was performed in 29 patients in the PN group, and 7 in the RN group. The average time of renal vessel occlusion was 43 minutes.

Complications

With regard to complications after partial nephrectomy, 2 patients developed postoperative urinary fistulae, which were resolved with indwelling of a double J-type ureteral stent. One patient with a normal left kidney developed renal hypertension and proteinuria at 6 months after right partial nephrectomy. The surgical specimen of right nephrectomy revealed no obvious stenosis of the renal artery. However, hypertension and proteinuria disappeared after nephrectomy.

In the RN group, 2 patients developed post-operative paralytic ileus, which was improved by conservative management. Superficial surgical site infection and postoperative bleeding from the retroperitoneal space were found in one patient each in the RN group.

Table 2. Pathological findings for patients treated with partial nephrectomy and radical nephrectomy

	Partial nephrectomy (n=54)	Radical nephrectomy (n=51)	P-value
T1a	45	49	NS*
T1b	5	0	
T3a	4	2	
Grade 1	18	23	NS*
Grade 2	34	26	
Grade 3	2	2	
v (+)※	1	2	NS**
v. (−)	53	49	
N0		51	
N1≦		0	
Maximum diameter. mean mm.	27	29	NS*
Surgical margin. mean mm. (range)	5 (0–15)		

* Using the Mann-Whitney U-test. ** Using χ^2 test. NS: Not significant. ※ microscopic venous involvement.

Table 3. Operative outcomes of patients treated with partial nephrectomy and radical nephrectomy

	Partial nephrectomy (n=54)		Radical nephrectomy (n=51)	P-value
	Imperative (n=11)	Elective (n=43)		
Vessel-occlusion time. mean (range) min.	43			
	32 (0–60)	46 (0–88)		
Operation time. median (range) min.	245		213 (98–307)	NS*
	223 (105–345)	255 (127–342)		
Amount of bleeding. median (range) ml	600		390 (65–1,200)	P=0.02*
	630 (200–2,800)	580 (130–1,900)		
No. of homologous transfusion	2	5	5	NS**
No. of complications	3 (5.6)		4 (7.8)	NS**
	Urinary leakage: 2 Renal hypertension: 1		Ileus: 2 Surgical site infection: 1 Postoperative hemorrhage: 1	

* Using the Mann-Whitney U-test. ** Using χ^2 test. NS: Not significant.

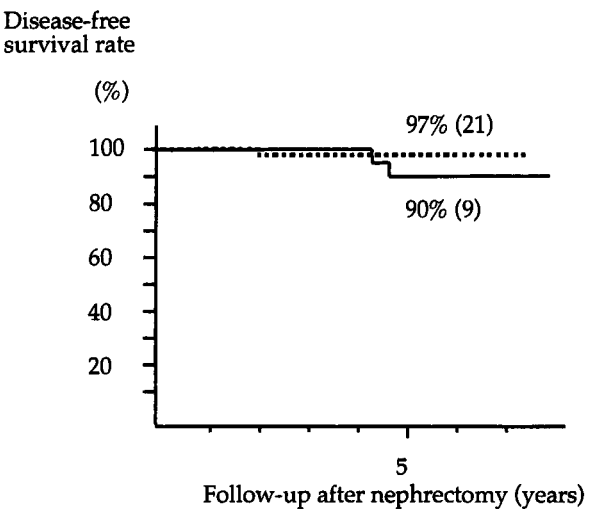

Fig. 1. Disease-free survival rates of patients treated with partial and radical nephrectomies. ( ): Number of patients at risk, —— Partial nephrectomy, ····· Radical nephrectomy.

Disease-free survival

Figure 1 shows the disease-free survival rates according to each procedure. The 5-year disease-free survival rates in the PN and RN group were 90% and 97%, respectively, without any significant difference. No patients died of cancer in either group. While no patients in the PN group had local recurrence originating from the resected area of the renal parenchyma, 2 patients in the PN group developed metastatic disease. One patient with an imperative indication had received partial nephrectomy for asynchronous RCC (pT1a, grade 2) in the upper pole of a solitary kidney. He developed recurrence in the lower pole of the operated kidney and single bone metastasis of the right tibia 4 years after partial nephrectomy, which were treated with partial nephrectomy again and radical resection of bone metastasis. The other patient (pT1a, grade 1) developed multiple metastases in the lung 4 years after surgery, which completely disappeared after treatment with interferon-α for one year. In the RN group, one patient with pT3a had local recurrence 22 months postoperatively and underwent surgical removal of the lesion. The patient continues to be disease-free 8 years after the last surgery.

Renal function

In all cases in the RN group and the elective cases in the PN group, preoperative serum creatinine was 1.5 mg/dl or less, except for 2 imperative cases in the PN group (1.6, 1.9 mg/dl) (Fig. 2). Immediately after surgery, no patients, even the imperative cases in the PN group, required specific treatment for impaired renal function. At 2 weeks after surgery, 7 (13%) of the 54 patients in the PN group had serum creatinine levels of greater than 1.5 mg/dl, and 11 (24%) of 50 patients, in the RN group (Fig. 2). The mean 24 h Ccr at 2 weeks after surgery was significantly lower than the mean preoperative level in both groups (124.4 vs. 101.3 *l*/day in the PN group and 116.0 vs. 74.1 *l*/day in the RN group). A study on the recovery of spared renal function, which was evaluated by renography with MAG-3, indicated that it tended to depend on the residual volume of the renal parenchyma (Fig. 3). Removal of one half of the parenchyma hampered recovery of renal function. However, patients with removal of less than one-third of the parenchyma achieved the expected function 3 months after the operation, depending on the remaining proportion of the parenchyma. A similar tendency was found for the change of the serum creatinine level (Fig. 2).

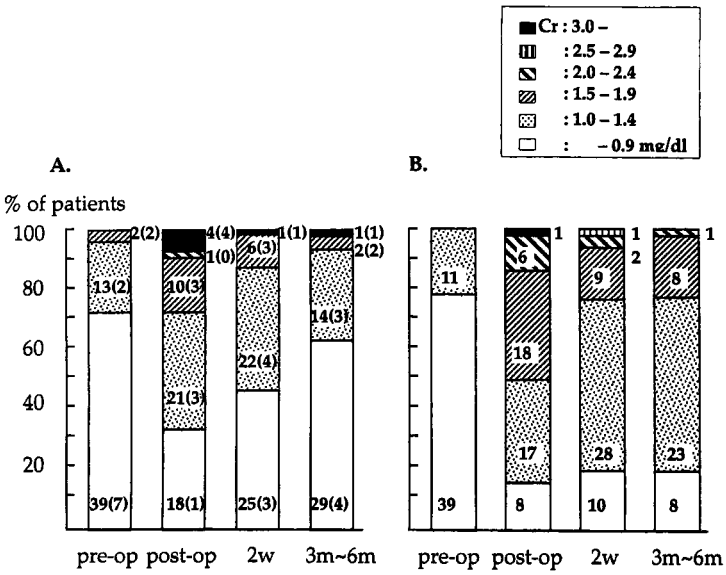

Fig. 2. Serum creatinine levels before and after the operation. A) Partial nephrectomy number of total cases (imperative case). B) Radical nephrectomy number of total cases.

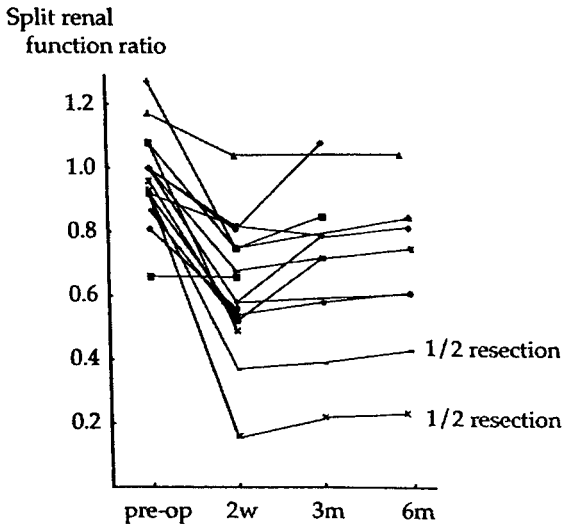

Fig. 3. Change of split renal function rate with time after partial nephrectomy. Split renal function ratio: ERPF of spared kidney/ERPF of normal opposite kidney.

Subsequently, all of the cases in the PN group maintained stable renal function throughout the period of follow-up. On the other hand, renal function of 2 cases in the RN group deteriorated slowly by 2 and 3 years after nephrectomy, respectively. Diabetic nephropathy was a cause of renal dysfunction in one patient, and surgery for an abdominal aortic aneurysm was in the other patient.

DISCUSSION

One of the potential problems with partial nephrectomy is the risk of local recurrence in the operated kidney. This is probably due to the growth of multifocal RCC and incompletely resected tumors. The reported incidence of local recurrence for tumors 4 cm or less in diameter is 0–3% and the incidence of multifocality is less than 5%[11]. The relationship between multifocality and local recurrence was neither linear nor predictable, which may be for the reason why the period of follow-up was short or that the tumors were clinically insignificant. To decrease the risk of local recurrence, excising an additional 1 cm margin of peritumor renal parenchyma could ensure a true negative margin[12] In addition, when the indication for partial nephrectomy is limited to renal tumors less than 4 cm in diameter, the risk of local recurrence could decrease significantly[5,13]. In our study, recurrence from the surgical margin did not occur in any patient with partial nephrectomy, but one patient developed recurrence in the ipsilateral kidney after surgery due to multifocality or metastasis from contralateral RCC that had previously existed. We did not observe any significant difference with respect to disease-specific or disease-free survival or cancer progression between the two groups regardless of the short follow-up. Several recent retrospective studies have shown long-term 5 and 10-year disease-free survival rates of 97% to 100% after partial nephrectomy for stage T1 tumors, especially those less than 4 cm in diameter[1–5] The cancer-specific survival rate is reported to be similar in patients undergoing radical nephrectomy and partial nephrectomy for localized RCC smaller than 4 cm[5,6] A prospective study that compared the results of patients who underwent nephron-sparing surgery with those who underwent radical nephrectomy yielded no difference in overall survival between the two treatment groups[14]. However, those data were not derived from a sufficient period of follow-up to draw a conclusion. Thus, we should evaluate the 10-year cause-specific survival and recurrence-free rate of our patients.

As another problem in partial nephrectomy, the surgical technique may be more demanding than radical nephrectomy. In our study, only 3 patients treated with partial nephrectomy developed complications, including urinary fistulae in 2 patients (3.7%) and renal hypertension in one patient (1.9%). Urinary fistula is the most common renal related complication after nephron-sparing surgery with a reported mean incidence of 6.5%[11] Fortunately, almost all fistulae can be managed by the observation or insertion of a ureteral stent, and we succeeded using stent placement. Although pathological findings could not identify the cause of renal hypertension, injury of the endothelium in the renal artery due to occlusion of renal vessels may have led to damage to the renal artery.

The major advantage of partial nephrectomy is preservation of renal function for patients with impaired renal function, as well as for patients with normal contralateral renal function. The contralateral kidney is likely to be diseased in 6% of patients[13] In these patients preservation of the ipsilateral kidney is important. Systemic diseases such as diabetes and hypertension, nephrotoxic chemotherapy for other neoplasms, and vascular disease are all potential reasons for considering preservation of the normal renal parenchyma over a long term. In our study, although most patients in the radical nephrectomy group maintained satisfactory and stable renal function, 2 patients developed renal dysfunction due to diabetes and vascular disease, respectively, although the preoperative renal function was in a normal range. However, a study suggested that patients with single normal kidney are not at increased risk for progressive impairment of renal function[15] Therefore, the risks and benefits of partial nephrectomy must be assessed according to individual situation, referring to systemic or local conditions that may affect future renal function.

Although we did not evaluate several factors such as ischemic time that affect residual renal function after partial nephrectomy, the recovery of renal function tended to depend on the residual volume of the renal parenchyma. In the study of Kondo et al.[16], tumor size had a significantly negative impact on the functional residual function in partial nephrectomy, suggesting that the residual volume of the renal parenchyma might be responsible for renal function after operation. A tumor size of 4 cm or less compared with those more than 4 cm in diameter is accepted for elective cases in partial nephrectomy based on cancer-free survival and the mutifocality of RCC[11].

A recent report based on questionnaires showed that the quality of life significantly improved in patients with more remaining renal parenchyma after nephrectomy[17] In other reports, the differences in postoperative quality of life between patients treated with radical nephrectomy and those with nephron-sparing surgery were evaluated by using the EORTC QLQ-C30. The nephron-sparing surgery was superior to radical nephrectomy in physical function[18]. When we evaluate the clinical outcomes of radical and partial nephrectomies, quality of life is an important subject that we must investigate in the future.

CONCLUSIONS

Partial nephrectomy was safely performed with preservation of renal function in all patients with RCC. Partial and radical nephrectomies proved to be equally effective treatment methods in terms of cancer control. Although a prospective randomized study over a long period would be more appropriate, we concluded that partial nephrectomy can be a standard procedure for appropriately selected patients with localized renal cell carcinoma less than 4 cm in size.

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和文抄録

腎細胞癌における腎部分切除術の臨床的検討

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当院において1992年から2001年までに腎細胞癌に対し，腎部分切除術を施行した54症例の臨床的検討を行った．絶対的適応患者は11名，選択的適応患者は43名であり，観察期間は中央値44カ月であった．根治的腎摘除術を施行した症例のうち，臨床病期 T1a の51症例を比較対象として，周術期合併症，手術前後の腎機能，再発率について検討を行った．術中の出血量は部分切除群の方が多いものの，同種血輸血の割合に関して差は認めなかった．両群には，病理学的所見，合併症に関して有意差はなかった．部分切除術後，2症例に尿瘻，1症例に腎性高血圧を認めた．部分切除術後の局所再発を認めず，5年非再発率に関しても両群に有意差を認なかった．術後の腎機能は両群とも安定していたが，根治的腎摘除後では，基礎疾患を有する2症例（糖尿病，腹部動脈瘤術後）において徐々に腎機能低下を示した．

以上より，小径腎細胞癌に対する腎部分切除術は，根治的腎摘除術と比較しても，安全で有用な治療法と考えられた．

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