

ORIGINAL ARTICLE

Outcomes of laparoscopic radical nephrectomy for elderly patients with localized renal cell carcinoma

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Summary

Purpose: This study was to compare the short- and long-term outcomes of elderly versus middle-aged patients with localized renal cell carcinoma (RCC) who had undergone laparoscopic radical nephrectomy.

Methods: Between January 2012 and January 2018, a total of 151 patients with localized RCC [54 patients aged 70 years and above (elderly group)] and 97 middle-aged patients (aged between 55 and 69 years; middle-aged group) who underwent laparoscopic radical nephrectomy due to localized RCC were included in this study. The short- and long-term outcomes of patients were compared between the groups.

Results: According to the baseline characteristics, median age (73 vs 61, $p=0.000$), Charlson comorbidity index (≥ 3 : 35% vs 19%, $p=0.035$), and American Society of Anesthesiologists score (III: 20% vs 8%, $p=0.006$) were higher in the elderly

group than in the middle-aged group. The differences in short-term outcomes, including operation time, intraoperative blood loss, transfer rate, postoperative 30-day complication rate, severity of complication, and pathological results were similar in both groups. Moreover, the tumor recurrence rates, overall survival (OS) and disease-free survival (DFS) were similar in the two groups. Multivariate analysis also showed that age was not an independent predictor for OS and DFS.

Conclusions: The outcomes of laparoscopic radical nephrectomy for localized RCC were similar in the elderly and middle-aged patients.

Key words: localized renal cell carcinoma, laparoscopic radical nephrectomy, laparoscopic surgery, outcomes

Introduction

Renal cell carcinoma (RCC) arises from the tubular epithelial cells in the renal parenchyma and is the most common cancer in the kidneys, accounting for 2-3% of all cancer cases in adults [1-3]. The majority of RCC are diagnosed in patients aged between 50 and 70 years [1-3]. Since localized RCC is not sensitive to radiotherapy or chemotherapy, the most important treatment modality for localized RCC is surgical resection [4-6]. Guidelines for the diagnosis and treatment of RCC published by authoritative organizations, such as the National Comprehensive Cancer Network (NCCN) [7] and European Association of Urology (EAU) [8], recom-

mend initial treatment with radical nephrectomy for patients with clinical stage I (T1N0M0) RCC who are not suitable for partial nephrectomy and for patients with clinical stage II (T2N0M0) RCC. Clayman et al completed the first laparoscopic radical nephrectomy in 1991 [9]. Laparoscopic radical nephrectomy has drawn much attention because of its minimal invasiveness and efficacy, as well as its potential to cause fewer trauma and bleeding, leading to faster postoperative recovery and a shorter length of hospitalization [10-16]. With the aging population and the wide adoption of medical imaging equipment, there is an increasing number

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of elderly patients diagnosed with localized RCC [17-24]. Surgical treatment for elderly patients with localized RCC has been controversial because the risk of surgery is greater in elderly than in non-elderly patients. Thus, the objective of this study was to compare the short- and long-term outcomes of elderly versus middle-aged patients with localized RCC who underwent laparoscopic radical nephrectomy.

Methods

Between January 2012 and January 2018, patients with localized RCC who underwent laparoscopic radical nephrectomy at our hospital and who met the inclusion and exclusion criteria listed below were included in the study. Inclusion criteria: (1) complete clinical and follow-up data, (2) without a history of previous treatment with radiofrequency ablation or cryoablation before laparoscopic radical nephrectomy, and (3) operable primary tumor. Exclusion criteria: (1) incomplete clinical and follow-up data, (2) previous nonsurgical treatment such as ablation before surgery, and (3) recurrent or metastatic tumor.

According to the age at the time of localized RCC diagnosis, the patients were divided into two groups as follows: 54 patients as elderly group (aged 70 years and above) and 97 as middle-aged groups (aged between 50 and 69). Laboratory examination, abdominal ultrasound, and chest and abdominal computed tomography (CT) were performed before surgery to determine the clinical stage and exclude distant metastasis, and bone scans and

positron emission tomography/computed tomography (PET-CT) examinations were performed as necessary to confirm the clinical stage [25-27]. Tumor size was measured as the longest diameter of each tumor in any single plane of the preoperative imaging study. Laparoscopic radical nephrectomy was performed only by the pure laparoscopic approach, not by hand or robot-assisted techniques [10]. Lymph node dissection was not performed. Comorbidities were evaluated using the Charlson comorbidity index. The tumor stage was based on the 7th edition of the TNM classification of RCC, which was proposed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). Histological subtypes were classified according to the UICC and AJCC recommendations and tumor grades were determined according to the grading system of Fuhrman. This study adopted a fast-track method for perioperative management. Detailed surgical procedures have been previously reported [10]. Patients did not receive adjuvant chemotherapy or radiotherapy [10].

The severity of postoperative 30-day complications was graded using the Clavien-Dindo classification, which ranks the severity of postoperative complications into 5 grades [28-34]. Mild complications are classified as grades 1 and 2, while severe complications are classified as grades 3, 4, and 5.

Follow-up status was evaluated using physical examinations, laboratory tests, chest CT and abdominal CT scans according to the surveillance protocols. Recurrence was defined as any new soft-tissue masses >10 mm that were previously undetected by CT; biopsy was not routinely performed to confirm the diagnosis

Table 1. Baseline characteristics of the two groups (n=151)

Characteristics	Elderly group (n=54) n	Middle-aged group (n=97) n	p value
Age (years), median (range)	73 (70-76)	61 (55-69)	0.000
Male	33	62	0.732
Female	21	35	
ASA score			0.006
I	24	64	
II	19	25	
III	11	8	0.035
Charlson comorbidity index			
≥ 3	19	19	
< 3	35	78	
BMI (kg/m ²), median (range)	20 (18-26)	21 (17-28)	0.248
Clinical stage			0.870
cT1aNOM0	3	5	
cT1bNOM0	11	19	
cT2NOM0	40	73	
Laterality			0.707
Left	25	48	
Right	29	49	

ASA: American Society of Anesthesiologists

[1-4]. Cancer recurrence was determined according to the clinical and radiological findings. Disease recurrence was categorized as local and distant (any evidence of disease outside the renal fossa, including visceral, bone, and lung metastases) [10-12]. Deaths were categorized as cancer-related death and other causes based on individual record review.

Overall survival (OS) was calculated from the date of laparoscopic surgery till the last follow-up visit or death from any cause. Disease-free survival (DFS) was calculated from the date of laparoscopic surgery till the date of cancer recurrence or death from any cause.

Statistics

Variables were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t*-test. For variables following non-normal distribution, data were expressed as median and range and were compared by Wilcoxon test.

Differences of non-parametric values were analyzed by Mann-Whitney *U* test. Differences of qualitative results were analyzed by chi-square test or Fisher exact test. Survival rates were analyzed using the Kaplan-Meier method and differences between two groups were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS and DFS. Univariate variables with probability values less than 0.10 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. All statistical tests were two-sided, with the threshold of significance set at $p < 0.05$ level. Statistical package for social sciences (SPSS) version 13.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. This study complied with the Declaration of Helsinki rules and was approved by the Ethics Committee of our institution [approval number:201900112m, 12 January 2019].

Table 2. Surgical and pathological outcomes of the two groups (n=151)

Outcomes	Elderly group (n=54)	Middle-aged group (n=97)	p value
Conversion to open surgery, n (%)	1 (2.0)	2 (2.1)	1.000
Operative time (min), median (range)	160 (130-200)	150 (120-190)	0.321
Blood loss (mL), median (range)	130 (80-210)	110 (70-190)	0.097
Blood transfusion (n)	1	1	1.000
Hospitalization (days), median (range)	11 (8-21)	9 (7-18)	0.108
Postoperative 30-day complications, n (%)	13(24.1)	19 (19.6)	0.518
Urinary retention	5 (9.3)	6 (6.2)	
Ileus	2 (3.7)	3 (3.1)	
Wound infection	1 (2.0)	2 (2.1)	
Fever	2 (3.7)	3 (3.1)	
Upper gastrointestinal bleeding	1 (2.0)	2 (2.1)	
Respiratory insufficiency	1 (2.0)	2 (2.1)	
Acute renal failure	1 (2.0)	1 (1.0)	
Major complications, n (%)	1 (2.0)	1 (1.0)	1.000
Intraoperative mortality, n (%)	0 (0.00)	0 (0.00)	-
Postoperative 30-day mortality, n (%)	0 (0.00)	0 (0.00)	
Pathological TNM stage, n (%)			0.994
pT1aN0M0	2 (3.7)	3 (3.1)	
pT1bN0M0	7 (13.0)	12 (12.3)	
pT2N0M0	36 (66.7)	67 (69.1)	
pT3aN0M0	9 (16.7)	15 (15.5)	
Fuhrman grade, n (%)			0.719
1	7 (13.0)	11 (11.3)	
2	21 (38.9)	39 (40.2)	
3	18 (33.3)	28 (28.9)	
4	8 (14.9)	19 (19.6)	
Histological subtype, n (%)			0.966
Clear cell	48 (88.9)	86 (88.7)	
Non-clear cell	6 (11.1)	11 (11.3)	
Lymphovascular invasion, n (%)	1 (2.0)	2 (2.1)	1.000
Sarcomatoid differentiation, n (%)	1 (2.0)	1 (1.0)	1.000
Positive surgical margins, n (%)	0 (0.00)	0 (0.00)	-

Results

Comparisons of preoperative baseline data between the two groups are shown in Table 1. The mean age, Charlson comorbidity index, and American Society of Anesthesiologists (ASA) score were higher in the elderly group than in the middle-aged group, whereas other preoperative baseline data did not show any statistically significant differences.

There was no mortality in postoperative 30 days in all groups, moreover, there were no statistically significant differences in terms of operative time, intraoperative blood loss, transfer rate, intraoperative and postoperative transfusion rates, length of hospitalization, and postoperative 30-day complication rate, degree of severity of complications and pathological findings (Table 2) between the two groups.

The median follow-up time in the elderly and middle-aged groups group were similar [(41 (range

4-72) and 44 (range 3-76) months, respectively, $p=0.027$]. During the follow-up period, deaths occurred in 9 patients in the elderly group, of which 8 due to tumor recurrence and 1 to ischemic stroke. There were 14 deaths in the middle-aged group, of which 13 were due to tumor recurrence and 1 was because of factors unrelated to the tumor (Table 3).

The rates of 5-year OS and DFS of the elderly and middle-aged groups were similar (OS rate 77 vs. 84%, $p=0.458$ and DFS 73 vs. 75%, $p=0.445$), respectively (Figures 1 and 2). Uni- and multivariate analysis showed that the TNM stage and Fuhrman grade were independent predictors of the OS and DFS (Tables 4,5).

Discussion

The results of this study indicate that treatment with laparoscopic radical nephrectomy in elderly patients with localized RCC could achieve

Table 3. Long-term outcomes of the two groups (n=151)

Outcomes	Elderly group (n=54)	Middle-aged group (n=97)	p value
Tumor recurrence, n (%)	10 (18.5)	15 (15.5)	0.628
Recurrence site, n (%)			
Local	1 (2.0)	3 (3.1)	
Distant	8 (14.8)	10 (10.3)	
Mixed	1 (2.0)	2 (2.1)	
Disease free survival (months), median (range)	22 (10-50)	24 (15-45)	0.287
Mortality, n (%)			0.714
Cancer-related recurrence	9 (16.7)	14 (14.4)	
Non-cancer-related diseases	8 (14.8)	13 (13.4)	

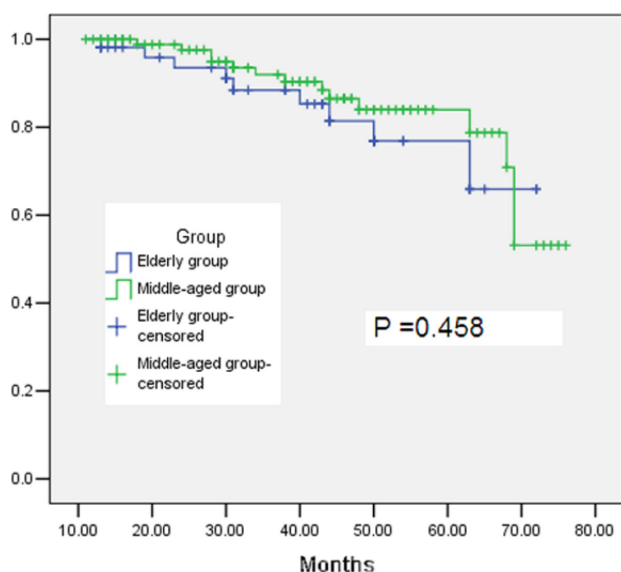


Figure 1. Comparison of overall survival rate between the elderly group (age ≥ 70 years) and the middle-aged group (≥ 55 and ≤ 69 years).

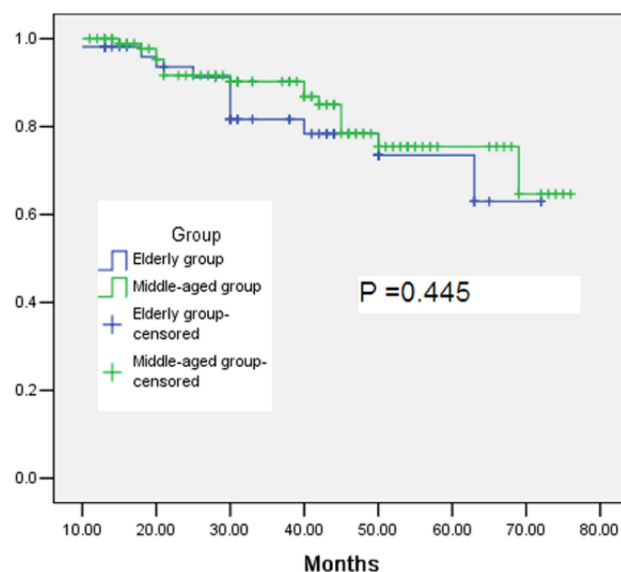


Figure 2. Comparison of disease-free survival rate between the elderly group (age ≥ 70 years) and the middle-aged group (≥ 55 and ≤ 69 years).

Table 4. Univariate analysis of overall survival and disease-free survival (n=151)

Variables	5-year overall survival (%)	p value	5-year disease-free survival rate (%)	p value
Age (years)		0.458		0.445
55-69	84		75	
≥70	77		73	
Gender		0.657		0.257
Male	85		76	
Female	79		71	
Charlson comorbidity index		0.094		0.115
≤ 3	90		79	
> 3	78		71	
ASA score		0.085		0.091
I-II	88		81	
III	75		73	
Histological subtype		0.641		0.480
Clear cell	85		76	
Non-clear cell	81		72	
Pathological stage		0.021		0.019
pT1N0M0	91		89	
pT2-3N0M0	74		70	
Fuhrman grade		0.035		0.020
1-2	88		75	
3-4	75		68	
Laterality		0.891		0.920
Left	84		75	
Right	81		71	

ASA: American Society of Anesthesiologists

Table 5. Cox proportional hazards model for overall survival and disease-free survival

Variables	5-year overall survival		5-year disease-free survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Charlson comorbidity index ≤ 3 vs ≥ 3	1.219 (0.584-2.544)	0.204	N/A	N/A
Pathological stage pT1N0M0 vs pT2-3N0M0	1.987 (1.321-2.988)	0.020	1.651 (1.202-2.268)	0.019
Fuhrman grade 1-2 vs 3-4	1.890 (1.458-2.450)	0.038	1.770 (1.234-2.539)	0.033
ASA score I-II vs III	1.157 (0.630-2.124)	0.314	1.108 (0.740-1.659)	0.250

ASA: American Society of Anesthesiologists

short- and long-term outcomes similar to those in middle-aged patients. The postoperative 30-day mortality and complication rates in the elderly group of the present study were lower than those reported in previous large-sample studies on open surgery, which fully demonstrated the minimally invasiveness of laparoscopic surgery [10-16]. In the present study, more than 20% of elderly patients had a Charlson comorbidity index score greater than 3 and an ASA grade III, but their short-term outcomes were similar to those of middle-aged patients. Long-term follow-up results showed that only a small number of patients in the elderly

group died of diseases unrelated to the tumor. The major cause of death was tumor recurrence, which further indicated that active treatment could improve the survival rates in elderly patients with localized RCC.

Treatment of stage T2 RCC with partial nephrectomy is currently controversial. Although some suggest that treatment of stage T2 RCC with partial nephrectomy is technically feasible [34-41], comparison with radical nephrectomy and partial nephrectomy has the following issues: (1) Unsatisfactory tumor control: the positive surgical margin rate of stage T2 RCC resected with partial nephrec-

tomy significantly increases. (2) Unclear benefit of renal function protection: the wound after resection of a stage T2 RCC tumor is large because of the large tumor size, which renders suturing and reconstruction difficult and also prolongs the warm ischemic time; this may increase the amount of normal renal parenchyma damaged during the resection and suturing process and therefore the extent of renal function preservation is unclear. (3) High incidence of surgical complications. (4) Most current studies on stage T2 RCC resected with partial nephrectomy are retrospective, case-control studies are limited by selection bias, a small sample size and short follow-up times, and they cannot provide high-quality evidence to support the use of partial nephrectomy [34-41].

Laparoscopic radical nephrectomy can be performed by either the transabdominal or retroperitoneal approach, both of which have advantages and disadvantages [42,43]. The transabdominal route enables a large operating space with a clear view of the anatomic layers, but there is a potential risk of damaging the abdominal organs [42,43]. The retroperitoneal route interferes less with the abdominal organs. It provides direct entry to the surgical field without the need to separate tissues, thereby causing little disturbance to abdominal organs [42,43]. The drainage is confined to the posterior abdominal cavity, which avoids contamination of the abdominal cavity and tumor implantation. However, the disadvantage of this approach is the small operating space and lack of clear anatomic markers. Therefore, this operation demands a high-level of technical skill and is difficult for beginners to master. Studies have shown that both routes achieve similar short- and long-term outcomes [42,43]. In clinical practice, the choice of surgical routes depends on the operator's habits and proficiency. In the present study, laparoscopic radical nephrectomy was performed via the retroperitoneal route, and its short- and long-term outcomes were similar to those reported in previous publications [42,43].

Fast-track surgery (FTS) refers to the use of perioperative treatment approaches validated by evidence-based medical research to minimize surgical-related stress, prevent organ dysfunction,

expedite patients' recovery and improve their prognoses, thereby providing higher quality medical outcomes [44-50]. In the past 20 years, surgeons in many developed countries have adopted and promoted the concept of FTS and have achieved significant results. The application of FTS in RCC surgery can expedite patient recovery after operation and ensure maximum medical safety [44-50]. Elderly patients are a high-risk population for radical nephrectomy, and the risks of postoperative complications and deaths are higher than in nonelderly patients [44-47]. In the present study, the results of postoperative complication rate, mortality rate, and length of hospitalization were similar in the elderly and middle-aged patient groups, which might be related to the application of the FTS concept.

The long-term outcomes, including tumor recurrence rate, OS rate, and DFS rate were similar in both groups of patients in this study. The results of this study are similar to those of previous reports [10-16]. There is, to the best of the authors' knowledge, no publication in the English language that has reported long-term outcomes of elderly patients with localized RCC treated with laparoscopic radical nephrectomy. This study demonstrates for the first time that elderly patients with localized RCC treated with laparoscopic radical nephrectomy can achieve long-term outcomes similar to those of middle-aged patients.

However, this study has several limitations. First, it was based on a single-center, and it is retrospective analysis, not a prospective randomized analysis. Second, the sample size was small, and the follow-up period was not very long. These limitations should be considered when interpreting our results.

In conclusion, treatment with laparoscopic radical nephrectomy for elderly patients with localized renal cell carcinoma does not increase postoperative complications and mortality and can achieve long-term outcomes similar to those in middle-aged patients.

Conflict of interests

The authors declare no conflict of interests.

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