Safety and outcomes of surgical treatment of renal cell carcinoma in the elderly

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Introduction: *Treatment of the elderly patient with a small renal mass is becoming a common conundrum with scant data available to support treatment decisions. Goals were to assess risk of surgical treatment for renal cell carcinoma (RCC) in the elderly as compared to their younger counterparts.*

Materials and methods: *A prospectively maintained database consisting of all renal tumors between August 2004 and November 2009 was utilized. Patients who underwent extirpative treatment for RCC were divided into groups based on age cutoff of < 75 and ≥ 75 years old. Primary outcome measures were likelihood of partial nephrectomy versus radical nephrectomy, complication rates, and overall and cancer-specific survival. A secondary outcome investigated was renal function.*

Results: *Of 347 patients identified, 273 were < 75, and 74 were ≥ 75 years old. The elderly group was less likely to undergo partial nephrectomy (26% versus 43%, p = 0.045). They also had a higher rate of pT3 disease (20% versus 11%, p = 0.018), worse baseline renal function (46 mL/min/m^2 versus 92 mL/min/m^2, p < 0.001) and a longer length of stay (3.5 days versus 2.2 days, p < 0.001). Complication rates and survival outcomes were similar between the groups. Only Eastern Cooperative Oncology Group (ECOG) ≥ 1 and Charlson index ≥ 2 predicted likelihood of experiencing a complication.*

Conclusions: *Despite a longer length of stay, renal surgery is safe in selected elderly patients with minimal comorbidity and good functional status. The elderly have reduced baseline renal function indicating nephron sparing should be chosen whenever possible, when surgical intervention is elected.*

Key Words: renal cell carcinoma, outcomes, aged, nephrectomy, complications

Introduction

The incidence of renal cell carcinoma (RCC) is increasing, with an estimated 61,920 patients being diagnosed with and 13,120 patients dying of RCC in 2010 in the United States.[1] Despite the favorable stage migration due to increased incidental discovery, the death rate from RCC continues to increase indicating a need to re-evaluate current treatment paradigms.[2] The discovery of incidental renal masses is increasing most in the elderly population[3] and with the addition of ablative therapies and surveillance strategies, there are many possible choices for treatment. Recent data suggest that elderly patients may have more aggressive renal tumors further complicating treatment choices.[4,5] Appropriate treatment of the elderly patient with a small renal mass is thus becoming a common conundrum with scant data available to support treatment decisions.

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Due to a recent understanding of the adverse effects of radical renal surgery on renal function and subsequent cardiovascular morbidity and mortality, guidelines advocate considering nephron sparing surgery (NSS) in all patients with small renal masses.[6] Because oncologic control is known to be similar to radical surgery, NSS is the treatment of choice for small renal masses in the general population.[7,8] Little is known regarding the risks and benefits of NSS specifically in the elderly.[9,10] NSS continues to be underutilized in the general population.[11,12] It is likely that this underutilization is more pronounced in the elderly due to fear of increased complications and a perceived decrease in benefits. To address this, rates of complications and cancer outcomes in elderly patients surgically treated for renal masses in a prospectively collected, single surgeon series were compared to that of younger patients from the same cohort.

Materials and methods

Following institutional review board approval, we utilized a single institution, prospectively maintained surgical database consisting of all renal tumor cases between August 2004 and November 2009. All patients who underwent extirpative treatment for renal cell carcinoma by one of three staff urologists were included. All surgically fit patients with a 5 year life expectancy were offered surgical treatment. Type of nephrectomy performed (laparoscopic or open and partial or radical) was at the discretion of the surgeon, but in general partial nephrectomy was preferred whenever surgically feasible and oncologically sound. Patients were divided into two groups based on age cutoffs of < 75 years of age (group 1) and ≥ 75 years of age (group 2). This age cut off was chosen based on life expectancy of < or > 10 years. Additional subgroup analysis was performed on patients with pathologic stage T1 tumors.

Clinical and surgical features evaluated included gender, Eastern Cooperative Oncology Group performance status (ECOG), Charlson comorbidity index (CCI), gender, tumor stage and grade, type of nephrectomy (open or laparoscopic, radical or partial), length of hospital stay, surgical time, estimated blood loss, vital status, 30 day and 90 day mortality rates, cause of death (if applicable), and time from cancer diagnosis to death. Type of nephrectomy performed (laparoscopic or open and partial or radical) was at the discretion of the surgeon, but in general partial nephrectomy was preferred whenever feasible and oncologically sound. Intraoperative, immediate postoperative (within 24 hours), delayed postoperative (24 hours to discharge), late postoperative (discharge to 30 days after surgery), and total complications were all reviewed and graded according to the Clavien classification.[13] Pre and postoperative estimated glomerular filtration rates (eGFR) were calculated using the Crockcroft-Gault model. In all patients, complete clinical and pathologic data were available at the time of review. All pathologic specimens were reviewed by a fellowship trained genitourinary pathologist and used the American Joint Committee on Cancer TNM staging system and World Health Organization grading system relevant to time of diagnosis.

Primary outcome measures were complication rates, overall survival (OS) and cancer-specific survival (CSS). A secondary outcome investigated was renal function as estimated by eGFR. Categorical variables were compared using chi-squared analysis. Parametric continuous variables were compared using the student's t-test and non-parametric variables were compared using the Wilcoxon rank-sum test. Univariable and multivariable logistic regression analyses were performed to evaluate variables associated with experiencing any complication. Cox proportional hazard modeling and Kaplan-Meier analysis were performed to evaluate OS and CSS. A p value of less than 0.05 was considered statistically significant. Analyses were performed using Stata software, version 11.0 (StataCorp, College Station, TX, USA).

Results

A total of 347 patients were identified with a median age of 64 (inter quartile range [IQR] 57-74), 205 (61%) of which underwent radical nephrectomy (RN) while 132 (39%) underwent partial nephrectomy (PN). One hundred seventy three patients underwent laparoscopic RN and 119 patients underwent laparoscopic PN. Of the 347 patients, 273 (79%) were < 75 years of age (group 1), while 74 (21%) were ≥ 75 years of age (group 2). Median age was 61 (IQR 53-67) in group 1 and 81 (IQR 77-85) in group 2. Groups 1 and 2 were similar in terms of gender distribution (65% male in each group, p = 0.996), ECOG (10.3% versus 9.45% ECOG ≥ 1, respectively, p = 0.556), CCI (53.0% versus 63.0% CCI ≥ 1, respectively, p = 0.130) and mean tumor size (5.8 ± 3.8 cm versus 6.2 ± 3.2 cm, respectively, p = 0.370). On pathologic analysis, group 2 had a slightly higher rate of venous involvement (11% versus 5%, p = 0.048) and resulting advanced pathologic stage, Table 1. Length of hospital stay was also longer in older patients (3.5 days versus 2.2 days, p < 0.001) while surgical times, estimated blood loss, Fuhrman grade and vital status were similar between the groups, Table 1.

TABLE 1. **Clinicopathologic characteristics by age group**

	Group 1	Group2	p value
No. type of surgery (%)			
Open RN	25 (9)	7 (9)	0.027
Open PN	10 (4)	3 (4)	
Laparoscopic RN	128 (47)	45 (61)	
Laparoscopic PN	104 (38)	15 (20)	
Other*	6 (2)	4 (5)	
Mean surgical time (SD)			
Minutes	214 (63)	222 (83)	0.372
Mean EBL (SD)			
Milliliters	517 (125)	280 (27)	0.081
No. stage (%)			
T1aN0M0	119 (44)	21 (29)	0.018
T1bN0M0	38 (14)	15 (20)	
T2N0M0	29 (11)	3 (4)	
T3N0M0	30 (11)	15 (20)	
T4N0M0	2 (1)	2 (3)	
N+M0	19 (7)	9 (12)	
M+	33 (12)	9 (12)	
No. Fuhrman grade (%)			
1-2	231 (53)	41 (57)	0.859
3-4	125 (47)	31 (43)	
Mean LOS (SD)			
Days	2.2 (2.2)	3.5 (4.1)	< 0.001
Vital status (%)			
Alive, NED	198 (78)	53 (75)	0.866
Alive with disease	24 (9)	8 (11)	
Dead other cause	4 (2)	2 (3)	
Dead disease	29 (11)	8 (11)	
Total	273	74	347

RN = radical nephrectomy; PN = partial nephrectomy; EBL = estimated blood loss; LOS = length of stay; NED = no evidence of disease
*includes incomplete resections and aborted nephrectomies

In group 1, 153 (57%) patients underwent RN, and 114 (43%) patients underwent PN, while in group 2, 52 patients (74%) underwent RN while only 18 (26%) patients underwent PN (p = 0.045). When analyzing only pT1 tumors, older patients were less likely to undergo PN compared to younger patients (OR 0.42, 95% CI 0.20-0.89, p = 0.024). Group 2 underwent laparoscopic approach (versus open) at a rate similar to group 1 (85.7% versus 86.9%, respectively, p = 0.797).

Complications were seen in 18% of group 1 and 23% of group 2, Table 2. The majority of postoperative complications were low grade (Clavien I-II) at 56% and 71% of complications in group 1 and 2, respectively. The odds of experiencing any type of complication was not significantly higher for the older group compared to the younger (OR 1.36, p = 0.333). No significant differences were seen in rates of high grade, low grade or total complications, Table 2. On univariable analysis, ECOG ≥ 1, CCI ≥ 2, larger tumor size, and type of nephrectomy (PN versus RN) were associated with likelihood of any complication (OR 3.33, p = 0.001, OR 1.64, p = 0.002, OR 1.11, p = 0.003 and OR 0.50, p = 0.023, respectively), while age group and surgical approach were not (p = 0.330 and p = 0.162, respectively). On multivariable analysis, only ECOG ≥ 1 and CCI ≥ 2 independently predicted the likelihood of experiencing any complication, Table 3. Preoperative size, nephrectomy type, surgical approach and age group were not independent predictors.

TABLE 2. **Complications and mortality by age group (group 1 used as referent)**

	Group 1 No. (%)	Group 2 No. (%)	OR (95% CI)	p value
Intraoperative	16 (6)	4 (5)	0.91 (0.30-2.83)	0.882
Immediate postoperative	5 (2)	4 (5)	3.06 (0.80-13.8)	0.101
Delayed postoperative	13 (5)	6 (8)	1.76 (0.65-4.81)	0.267
Late postoperative	22 (8)	5 (7)	0.83 (0.31-2.27)	0.711
Clavien I-II	23 (8)	10 (13)	1.79 (0.77-3.74)	0.190
Clavien III-V	18 (7)	4 (5)	0.81 (0.26-2.47)	0.710
Total complications	49 (18)	17 (23)	1.36 (0.73-2.54)	0.333
30 day mortality	1 (0.4)	1 (1.4)	3.72 (0.23-60.2)	0.354
90 day mortality	3 (1.1)	1 (1.4)	1.23 (0.13-12.0)	0.857

Group 2 had a lower preoperative eGFR (45.7 mL/min/m^2 versus 92.3 mL/min/m^2, $p < 0.0001$) and a larger percent decrease in eGFR after surgery which was not statistically significant (20.8% versus 18.1%, $p = 0.233$). Group 2 did however have an increased rate of new onset stage ≥ 3 chronic kidney disease at 42.9% versus 18.7% ($p = 0.009$). As expected, RN resulted in a larger decline in eGFR and increased rate of new onset stage ≥ 3 chronic kidney disease as compared to PN for all patients, Table 4.

Median follow up was 11 months (IQR 4-25). The 30 day (0.4% and 1.4%, $p = 0.354$) and 90 day mortality rates (1.1% and 1.4%, $p = 0.857$) were similar between groups 1 and 2, respectively, Table 2. The 2 year OS was 78.9% and 76.4% and the 2 year CSS was 80.0% and 81.3% for groups 1 and 2,

TABLE 3. **Multivariable analysis: likelihood of any complication**

	OR	95% CI	p value
Age group			
1 (< 75)	Referent		0.124
2 (≥ 75)	1.70	0.86-3.33	
ECOG			
0	Referent		0.042
≥ 1	2.36	1.03-5.42	
Charlson index			
0	Referent		0.016
1	0.76	0.30-1.91	
≥ 2	2.17	1.16-4.08	
Size			
1 cm increase	1.05	0.96-1.15	0.293
Type nephrectomy			
RN	Referent		0.762
PN	0.89	0.41-1.95	
Surgical approach			
Laparoscopic	Referent		0.700
Open	1.17	0.52-2.66	

ECOG = Eastern Cooperative Oncology Group; RN = radical nephrectomy; PN = partial nephrectomy

TABLE 4. **Estimated glomerular filtration rate after nephrectomy by age group**

	Group1	Group 2	p value	RN	PN	p value
Mean preoperative eGFR*	92.3	45.7	< 0.001	78.0	90.6	0.005
Mean postoperative eGFR	76.9	41.7	< 0.001	62.8	81.2	< 0.001
% decrease in eGFR	18.1	20.8	0.233	23.2	11.5	< 0.001
% new onset stage ≥ 3 CKD	18.7	42.9	0.009	27.6	14.0	0.012

eGFR = estimated glomerular filtration rate
CKD = Chronic kidney disease
*mL/min/m^2

respectively. No significant differences were seen in OS or CSS between the groups (HR 1.01, 95% CI 0.50-2.05, p = 0.979 and HR 0.93 95% CI 0.43-2.04, p = 0.858, respectively), Table 1 and Figure 1. The small sample size precluded further survival analysis by pathologic stage or type of surgery.

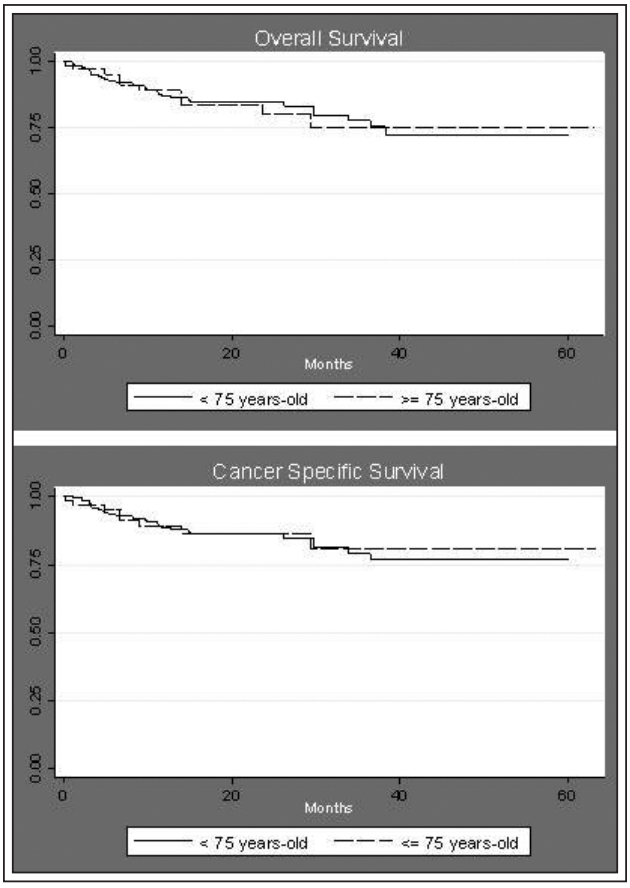

Figure 1. Overall and cancer-specific survival in surgical kidney cancer patients by age group.

Discussion

Over the past decade, the average size of renal masses has steadily decreased while the discovery of incidental masses is increasing most in the aged population.[2,3] Urologists are increasingly faced with the dilemma of what is the appropriate treatment of the elderly patient with a small renal mass. Treatment options are now numerous, including partial or radical extirpative surgery, ablative therapies and surveillance strategies, which further complicates the paradigm. Due to a recent understanding of the increased mortality associated with chronic kidney disease resulting from radical kidney surgery,[14] American Urological Association guidelines advocate the use of NSS for the majority of T1 lesions in the general population.[6] Treatment strategies need re-evaluation in light of the continued increase in mortality from RCC, despite downward stage migration.[2] Indeed age was an independent predictor of cancer specific survival in two series indicating suboptimal treatment of RCC in the aged population.[4,15] In order to better understand the risks and benefits of surgical treatment for renal masses in the elderly we undertook this comparative analysis of complications, functional outcomes and cancer-specific outcomes of patients treated surgically for RCC, grouped by age < or ≥ 75 years of age.

Higher pathologic stage was seen in the older cohort, which has been found in several prior studies.[4,5] The substantiation of this finding is worrisome as treatment strategies in the elderly often include ablative therapies and surveillance, which are less durable than extirpative treatments in high risk disease.[15,16] Furthermore, if surveillance or ablation is undertaken, an accurate assessment of pathologic stage and grade is rarely obtained.[16] Cancer in general is treated less aggressively in the elderly, which is appropriate if life expectancy is shortened by competing mortality risks. Analyzing the Surveillance, Epidemiology and

End Results database, Kutikov et al have suggested a nomogram for predicting mortality from renal cell versus from other cancers or other non-cancer causes.[17] This type of assessment will aid in making treatment decisions regarding the small renal mass in the elderly and should supplant decisions based on age alone.

As expected, PN was utilized less often in the elderly population (26% versus 43%). However, we found no increase in total complications in the elderly. Type of nephrectomy was not independently associated with rates of complications indicating that in experienced hands PN can be performed safely. Elderly patients may need longer recovery, as indicated by the longer LOS. This should not however, preclude surgical treatment in select elderly patients with good functional status and minimal comorbidities. Others noted the underutilization of PN in the elderly and found that age was an independent predictor of radical surgery over PN in large populations, despite controlling for comorbidities.[14,18] This indicates that absolute age remains inappropriately important in the treatment decision-making process. We found that high ECOG and CCI were associated with increased complications rather than age group. In comparisons of outcomes of laparoscopic and open RN, and open PN in the elderly, complications were similar to younger counterparts.[9,19,20]

Others have tried to sort out benefits of the various treatments for RCC in the elderly. In a recent examination of 537 patients aged ≥ 75 years treated with either surveillance, nephron sparing intervention (ablation or PN) or RN, 5 year overall survival was poorest in the surveillance group (58%) as compared to the nephron sparing group (76%) and the RN group (72%).[15] This however likely represented selection bias as the surveillance group was significantly older with more comorbid conditions than the other groups. Treatment type was not independently associated with OS, CSS or cardiovascular mortality, making drawing conclusions about which treatments were preferred difficult.

The current series is limited in that cohorts of elderly patients who have undergone surveillance or ablation were not available for comparison or for understanding the proportion of all patients that underwent surgery in either group. The retrospective nature also has inherent selection bias for more surgically fit candidates. The extent to which selection bias played a role in pathologic outcomes of the elderly group is unclear and thus these findings must be approached with caution. In addition, the small size of the elderly group may not have provided sufficient power to determine if there is truly no difference in complication rates versus the younger group. However, there were a number of complications in both groups with overall rates being very similar. This lends support to the assertion that well selected elderly patients can safely undergo surgery. Further research efforts should be directed at larger populations of elderly patients where complication data is available in order to substantiate this finding. The purpose of the analysis was to investigate surgical, renal function and intermediate term oncologic outcomes of surgically treated elderly renal cell patients, in order to demonstrate that perioperative outcomes of elderly patients are at least non-inferior to those of younger counterparts, which we believe was accomplished.

To date data support that, if carefully selected based on comorbid status, rather than absolute age, the elderly can safely undergo surgical treatment of their renal masses. Surveillance remains a viable option but with several caveats. Long term outcomes of surveillance remain unknown. Furthermore, the elderly may have a higher likelihood of having high risk disease as seen in this cohort and several others.[4,5,21] Metastasis has been reported even in masses less than 3 cm in size.[16] As in prostate cancer, identifying indolent disease is difficult without pathologic data. Percutaneous biopsy of renal masses underestimates grade[22] which may lead to elderly patients with aggressive tumors being inappropriately placed on surveillance. The growth rate during surveillance is variable and the rate of upstaging unknown.[23] A window of opportunity for NSS may be missed if surveillance protocols are not rigorous. Emerging data in prostate cancer literature also suggests an impact on quality of life and possibly increased rates of suicide related to a diagnosis of cancer.[24,25] These quality of life concerns may become an issue also with untreated RCC.

Which surgical therapy should be undertaken to treat RCC in the elderly remains in debate. NSS should be utilized whenever possible particularly in the elderly. Age has been shown to independently predict development of chronic kidney disease stage 3 after PN, ablation or RN indicating the high risk in this population regardless of treatment.[26] As seen in the present cohort the elderly have reduced renal reserve before treatment. Moreover, rapid decline in eGFR is associated with all cause and cardiovascular mortality in the elderly.[27] If surgery is chosen radical surgery should be a last resort.

Conclusions

Despite a longer LOS, renal surgery is safe in selected elderly patients with minimal comorbidity and good functional status. Treatment of RCC in the elderly should include consideration of surveillance, ablation, and surgical extirpation. The elderly have reduced baseline

renal function indicating PN should be chosen whenever possible, when surgical intervention is elected. Treatment decisions regarding renal masses in the elderly should be based on functional and comorbid status, competing risks assessment and patient preference, rather than on patient age alone. □

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