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ORIGINAL ARTICLE

# Active surveillance for incidental renal mass in the octogenarian

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**Abstract**
*Objective* To evaluate the oncologic outcomes among a large cohort of octogenarian patients placed on active surveillance for a localized renal mass.
*Methods* We retrospectively reviewed patients ≥80 years of age presenting for asymptomatic, incidentally detected clinically localized stage T1 renal mass between 2006 and 2013 who were followed by active surveillance (AS). The primary endpoint was development of metastatic renal cell carcinoma. Secondary outcomes included intervention-free survival, cancer-specific survival, and overall survival.
*Results* Eighty-nine octogenarians (median age = 83.4 years) were placed on AS for a median 29.9 months. Median Charlson Comorbidity Index and Katz Index of Independence in Activities of Daily Living scores were 2 and 5, respectively. For all comers, median initial tumor size was 2.4 cm with median growth rate of 0.20 cm/year. Eight (9.0%) patients failed AS due to delayed intervention and three (1.1%) due to systemic progression after median follow-up of 27.8 and 39.9 months, respectively. Two (2.2%) patients in the delayed intervention cohort developed metastasis after treatment. Tumor growth rate was significantly higher among those undergoing intervention versus no intervention (0.60 vs. 0.15 cm/year, $P = 0.05$) and among patients with systemic progression versus no metastasis (1.28 vs. 0.18 cm/year, $P = 0.001$). Five-year intervention-free, metastasis-free, cancer-specific, and overall survivals were 90.6, 95.6, 95.6, and 85.7%, respectively.
*Conclusion* AS represents an effective management strategy in octogenarians given low overall risk of metastasis. Tumor growth kinetics may identify patients at risk of systemic progression in whom treatment should be considered.

**Keywords** Watchful waiting · Renal cortical neoplasms · Extirpative surgery · Small renal masses · Renal cell carcinoma · Kidney cancer

## Introduction

Increased utilization of abdominal imaging has led to a rise in the incidental detection of localized renal masses [1–3]. As many of these lesions follow an indolent course, a movement toward observation over intervention has been suggested [4]. This conservative approach to management has been slow to gain acceptance by patients and clinicians due to a paucity of metrics that reliably identify patients at risk of progression and those who may benefit from intervention [5].

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Octogenarians constitute a challenging population in whom clinical dilemma exists regarding the benefits of treating incidentally detected renal masses. Actuarial life expectancy and higher theoretical risk of surgical morbidity offer a compelling argument to observe incidentally detected renal tumors in the elderly [6–8]. However, the octogenarian age is not synonymous with limited life expectancy as several studies demonstrate this population to constitute a heterogeneous cohort with many being of good functional status and possessing few comorbidities [9, 10]. In view of the poor clinical outcomes associated with progression of RCC, primary surgical therapy remains the preferred management option [11]. Yet, the higher pathologic aggressiveness and malignant potential of renal masses in patients aged 75 and older further support the role of intervention [12].

No study has evaluated surveillance protocols in an exclusively octogenarian cohort. Extrapolation of clinical outcomes from trials involving relatively younger patients to an older population can be misleading [13–15]. Moreover, assessments of surveillance protocols in the elderly often encompass patients of relatively poor performance status; observations among those with many comorbidities may not translate over to healthier elderly patient groups as are present in our study cohort. In this study, we evaluated the clinical course of octogenarian patients placed on AS for incidentally detected clinical stage T1 renal masses. Tumor characteristics and patient functional status were assessed to identify predictors of surveillance failure and disease progression.

## Patients and methods

After institutional review board approval, data on patients evaluated for a renal mass at our institution between 2006 and 2013 were retrospectively reviewed. Patients $\geq$80 years of age at initial visit for a radiographically diagnosed enhancing solid renal mass were considered for inclusion. The study database contained patients' age, gender, body mass index, comorbidities, tobacco use, and tumor characteristics (laterality, size at maximal cross-sectional dimension on the radiologic study, R.E.N.A.L. nephrometry score). CCI and ADL were determined for all patients. Octogenarians placed on surveillance for a clinically localized solitary mass $\leq$7.0 cm (cT1N0M0) comprised the final study cohort. Exclusion criteria included the presence of a solitary kidney, prior history of renal cell or upper tract urothelial carcinoma, known diagnosis of hereditary syndromes associated with RCC, previous extirpative or ablative procedure of the kidney, metastatic disease at time of diagnosis, and presence of an active non-RCC malignancy. The decision to pursue AS was at the patient's and physician's discretion after discussion of all treatment options.

The AS protocol specified in the National Comprehensive Cancer Network guidelines was used for all patients and included baseline staging workup with cross-sectional imaging of the abdomen and pelvis and X-ray or CT of the chest [16]. Patients were followed with at least 2 serial images performed over a minimum period of 6 months. No masses were biopsied prior to AS. Follow-up cross-sectional imaging of the abdomen and pelvis and surveillance chest X-ray were performed at their 6-month visit and at least annually thereafter. Further studies (e.g., blood chemistry, bone scan, brain imaging) were performed where clinically indicated at the discretion of the urologist. There were no established criteria for the initiation of delayed therapy; however, tumor growth rate was the primary metric that influenced management decisions for all participating providers. Tumor size was measured at the maximal cross-sectional dimension by the radiologist and/or urologist. Dictated reports were not used in this study. Final tumor size was defined as the largest linear diameter of the lesion on most recent imaging study or the largest diameter of the tumor on the pathologic specimen for those managed with delayed extirpative therapy. Change in mean diameter per unit time was calculated to determine tumor growth rate in a manner that accounted for differences in imaging intervals.

The primary endpoint analyzed was the development of metastatic RCC. Secondary outcomes were cancer-specific survival, overall survival, and the utilization of delayed intervention after an initial trial of surveillance. Death was attributed to RCC in patients who had systemic progression of their renal lesion, unless metastasis was proved by biopsy to be related to another malignancy. Differences between patients who remained on AS and those who underwent delayed intervention or developed metastasis were evaluated in an effort to identify predictive factors.

Descriptive statistics are reported as median and interquartile range for continuous variables and frequency and percentages for categorical variables. The Mann–Whitney–Wilcoxon $U$ test was used for comparing the medians of continuous variables, and Chi-square and Fisher's exact test was used to compare incidences for categorical variables. All tests were two-tailed, and a $p$ value $<0.05$ was considered statistically significant. All analyses were performed using STATA version 13.0 (Statacorp, College Station, TX, USA).

## Results

Between 2006 and 2013, 179 octogenarians presented to our institution with an asymptomatic, incidentally detected

cT1 renal mass. Eighty-nine patients placed on AS were included in our study cohort. The remaining patients underwent immediate treatment (within 6 months of diagnosis); 13 patients were managed by cryoablation, 31 by partial nephrectomy, and 33 by radical nephrectomy. Thirteen patients were excluded due to surveillance for <6 months or poor follow-up data.

Patient demographics and clinical characteristics are delineated in Online Resource 1. Median age of octogenarians at initiation of AS was 83.4 years. The majority of the study population exhibited a low comorbidity profile, with the calculated CCI having been ≤2 in 69 (77.5%) patients. Additionally, 52 (58.4%) patients demonstrated optimal function with regard to basic activities of daily living (ADL = 5 or 6). Thirteen tumors were cT1b with the remainder being cT1a. Median tumor size at initiation of AS was 2.4 cm [interquartile range (IQR) 1.7–3.5 cm] with median overall growth rate having been 0.20 cm/year (IQR 0.03–0.57 cm/year) for all lesions (Table 1).

Nine (10.1%) patients failed AS due to delayed intervention in eight (9.0%) patients and systemic progression while on surveillance in one (1.1%) patient (Online Resource 2). Two (2.2%) patients developed metastatic RCC after delayed intervention at 9.8 and 5.8 months postoperatively. Median duration to systemic progression and delayed intervention was 39.9 months (IQR 28.1–42.9 months) and 27.8 months (IQR 19.7–35.9 months), respectively (Table 1).

Laparoscopic partial or radical nephrectomy was performed on patients who underwent delayed treatment except in one case where cryoablation was utilized. Pathology and clinical outcomes for the delayed intervention cohort are delineated in Online Resource 2. RCC was observed in all except one case. Delayed intervention was considered in six patients due to increased tumor growth rate, whereas treatment in the remaining two patients was a patient-driven decision. Tumor growth rate was significantly higher among those undergoing delayed intervention compared to patients continuing AS (0.60 vs. 0.15 cm/year, $P = 0.05$; Table 1). No significant difference in initial tumor size, final radiographic tumor size, median nephrometry score, CCI, and ADL was observed between these groups (Table 1). Kaplan–Meier analysis revealed 5-year metastasis-free and intervention-free survival to have been 95.6 and 90.6%, respectively (Online Resource 3).

Tumor growth rate was significantly higher among octogenarians who developed systemic progression compared to patients whose tumors did not metastasize (1.28 vs. 0.18 cm/year, $P = 0.001$; Table 1). Similarly, median final radiographic tumor size was significantly greater in the metastatic cohort (5.3 vs. 3.3 cm, $P = 0.049$; Table 1). No significant difference in initial tumor size, median nephrometry score, CCI, and ADL was observed between these groups (Table 1). All patients who developed metastatic RCC died of disease. All-cause and cancer-specific mortality was 14.6% ($n = 13$) and 3.4% ($n = 3$),

**Table 1** Tumor characteristics based on outcome

| Variable | All patients ($N = 91$) | No intervention ($N = 83$) | Delayed intervention ($N = 8$) | No metastasis ($N = 88$) | Metastatic progression ($N = 3$) | $P$ |
|---|---|---|---|---|---|---|
| Initial tumor size (median ± IQR), cm | 2.40 (1.70–3.50) | 2.30 (1.70–3.60) | 2.45 (1.9–2.63) | – | – | 0.990 |
| | | – | – | 2.4 (1.70–3.50) | 2.0 (1.5–3.3) | 0.827 |
| Final tumor size (median ± IQR), cm | 3.3 (2.00–4.3) | 3.2 (2.00–4.30) | 3.80 (3.70–4.90) | – | – | 0.165 |
| | | – | – | 3.3 (2.00–4.28) | 4.90 (4.30–6.15) | 0.049* |
| Growth rate (median ± IQR), cm/year | 0.20 (0.03–0.57) | 0.15 (0–0.50) | 0.60 (0.55–0.85) | – | – | 0.050* |
| | | – | – | 0.18 (0.01–0.56) | 1.28 (0.91–1.69) | 0.001* |
| Follow-up duration (median ± IQR), months | 29.9 (16.1–42.9) | 29.9 (14.2–43.6) | 27.8 (19,7–35.9) | – | – | 0.579 |
| | | – | – | 29.8 (14.8–42.6) | 39.9 (28.1–42.9) | 0.955 |
| R.E.N.A.L. nephrometry score (median ± IQR) | 5 (4–5) | 5 (4–5) | 5 (4–5) | – | – | 0.913 |
| | | – | – | 5 (4–5) | 5 (4–5) | 0.227 |
| CCI (median ± IQR) | 2 (1–3) | 2 (1–3) | 2 (2–3) | – | – | 0.122 |
| | | – | – | 2 (1–3) | 2 (1–2) | 0.317 |
| Katz ADL (median ± IQR) | 5 (2–6) | 5 (2–5) | 5 (5) | – | – | 0.120 |
| | | – | – | 5 (2–6) | 5 (5) | 0.242 |

*ADL* activities of daily living, *IQR* interquartile range

* Statistical significance, $P \leq 0.05$

respectively, over the duration of the study (Online Resource 3). Median duration to all-cause and cancer-specific mortality was 40.9 months (IQR 20.1–54.6 months) and 43.0 months (IQR 25.3–56.1 months). Five-year overall survival and cancer-specific survival in this cohort were 85.7 and 95.6%, respectively (Online Resource 3).

## Discussion

The perceived low propensity for development of metastatic disease in patients with an incidentally detected cT1 renal mass has led to the preferential use of AS among elderly patients [4]. However, many studies that cite a low risk of systemic progression draw their conclusions from patient populations with a relatively broad age distribution [13–15]. The more aggressive nature of lesions in elderly patients, specifically those aged 75 years and older, necessitates a thorough understanding of the clinical impact associated with nonintervention in this group [12, 17].

We observed a low overall rate of progression among octogenarians surveilled for clinically localized renal mass, the incidence of metastasis having been 3.4% over a median follow-up of 39.9 months. Nevertheless, our study results demonstrate that this age group is not immune to the development of systemic disease. Metastasis occurred more frequently in our octogenarian cohort compared to other studies of AS, which were generally comprised of patients with a broader age distribution [13–15, 17, 18]. Crispen et al. [13] and Rosales et al. [14] cite the incidence of systemic progression to have been 1.3 and 0.5%, respectively, in the largest of series evaluating AS outcomes for incidental renal mass. However, these findings should be interpreted in the context of a lower median age for their study populations, 71 versus 83.4 years in our cohort.

Histologic review of a large number of nephrectomy specimens revealed significantly more higher-risk pathologic features in elderly patients above 75 years of age undergoing extirpative therapy for a renal mass [12]. In accordance with this observation, several reports demonstrate age >75 years to signify increased risk of systemic progression and cancer-specific mortality among patients managed with surveillance [17, 19]. As such, inclusion of younger patient groups, specifically <75 years of age, may obscure the prognostic significance of incidental renal masses among elderly patients due to a greater proportion of both pathologically and clinically indolent lesions. A systematic review of 880 patients managed with AS revealed the median age of the 18 (2%) patients who developed metastasis to have been 78 years [17]. These results reinforce the notion that renal neoplasms have higher malignant potential in elderly patients.

It is critical that the steady rise in life expectancy be considered in the management algorithm for the octogenarian patient. Since an initial study by Manton et al. formally acknowledged increased overall survival for octogenarians in the USA, several contemporary reports have corroborated these findings [9, 10]. In our series, the incidence of all-cause mortality was 14.6% over a 39.9-month follow-up period, with the incidence of death unrelated to RCC having been 11.2%. These findings are in contrast to several surveillance studies in which competing-cause mortality rates among elderly patients have been cited to be as high as 30% [6, 20]. Discrepancy in mortality rates likely relates to differences in the functional profile and health status of elderly patients studied. The trigger for placing a patient on AS in many reports often extends beyond old age encompassing an unfavorable comorbidity index, which may preclude safe intervention [14, 18, 20, 21]. In this respect, the oncologic significance of renal masses is more readily obscured by competing causes of mortality, supporting the role of observation with AS.

We report on the natural history of localized T1 renal masses in an octogenarian cohort comprised of many with good performance status and favorable comorbidity profile. Over a median follow-up of 39.9 months, the incidence of systemic progression was observed to have been 3.4%—patients who all subsequently died from RCC. Although overall risk of cancer-specific mortality was low, it was not overwhelmingly eclipsed by non-RCC causes of mortality, as has otherwise been shown to be the case among octogenarians with poorer performance status. According to the Centers for Disease Control Life Tables, people of octogenarian age could expect to live an additional 9 years [22]. Similarly, actuarial models from the US Social Security Administration calculate an additional life expectancy of 7.1 years for a patient who is 83.5 years of age [23]. In this context, the observed survival rate of 85.7% is in concordance with the improved overall survival rates of contemporary octogenarian cohorts. As such, there may exist oncologic benefit in identifying those octogenarians who are at greatest risk of progression.

Tumor growth kinetics are a commonly utilized surrogate for metastatic potential. A systematic review by Smaldone et al. [17] found the average linear growth rate to have been 0.8 cm/year for tumors following an adverse clinical trajectory versus 0.3 cm/year for indolent lesions. These findings are consistent with our observations, which demonstrated significantly higher growth rates for lesions that metastasized after a period of surveillance compared to those that remained localized (1.28 vs. 0.18 cm/year, respectively). Ideally, knowledge of factors associated with progression should facilitate timely delivery of treatment. Among eight octogenarians who underwent delayed intervention for lesions demonstrating accelerated growth, two

patients experienced metastatic progression. It is difficult to ascertain whether any oncologic benefit was derived from intervention as the natural history of treated lesions is unknown. However, it is important to consider that several surveillance studies report low overall rates of progression and cancer-specific mortality in the setting of delayed extirpative therapy for lesions with similar growth behavior [14, 17, 19]. A recurrence-free and cancer-specific survival benefit to partial nephrectomy versus AS for small renal masses has also been observed specifically among patients >75 years of age, but not younger cohorts, alluding to not only the more malignant nature of these lesions, but also the greater potential for clinical gain in treating suspicious lesions in the octogenarian [19]. Nevertheless, metastasis and cancer-specific death having occurred in two patients despite intervention underscore the need for more sensitive metrics to predict risk of tumor progression among octogenarians placed on AS for incidental renal mass.

A diagnostic role for biopsy of renal masses has been suggested in view of a 20% overall incidence of benign histology and the predominance of low-grade lesions with relatively low intrinsic malignant potential [24]. The clinical utility of renal mass biopsy is tempered by findings from a recent report that demonstrates a low discriminatory capacity for tumor grade; a study by Jeon et al. [24] found tumor grade to have been indeterminate in 68.7% of biopsies in which malignant disease was identified. Additionally, a high likelihood for non-diagnostic biopsy was reported for masses <2 cm, limiting the evaluation of over 40% of tumors in our cohort, including lesions which demonstrated systemic progression as their median initial size was 2.0 cm [24]. As pathologic stage and grade are important tumor metrics that convey progression potential, the limited capacity of renal mass biopsy to discern these parameters compromises its negative predictive value in octogenarians, a cohort in whom renal masses harbor more adverse phenotypic features than seen in younger age groups.

There are several limitations to this study aside from its retrospective nature. We investigate outcomes in a relatively small population of octogenarians with intermediate duration of follow-up, which may have precluded accurate assessment of progression risk and growth kinetics. The relatively small event rate precluded multivariable analyses to discern factors independently associated with intervention and progression. Additionally, outcomes could not be sub-stratified based on clinical stage because of the limited sample size. As renal mass biopsy was not utilized prior to initiation of surveillance to discern malignant from benign histology, our data may underestimate rates of RCC progression in this cohort [16, 24]. Although there were no defined set points for delayed intervention, our results may serve as a primer for future investigation of optimal growth rate cutoffs in the octogenarian population. Additionally, morbidity and mortality risk associated with various treatment strategies may mitigate the clinical significance of systemic progression in this population and thus require further study. Lastly, we do not evaluate outcomes among those who underwent delayed extirpative therapy in our series; however, it is interesting to note that no deaths in this cohort were attributable to non-RCC-related processes.

## Conclusion

AS is a safe and effective strategy for the management of clinical stage T1 renal mass in the octogenarian. Although there exists a low overall risk of metastasis and cancer-specific mortality, octogenarians, particularly those with a favorable performance and health profile, are not immune to clinical progression given improved longevity and higher pathologic aggressiveness of lesions. Tumor growth kinetics appear to correlate with propensity for systemic spread and may be utilized to discern those who require treatment.

**Author contributions** KEC performed data collection, data management, manuscript writing; PHS participated in project development, data management, statistical analysis, manuscript writing; VRP took part in data management; DMM participated in statistical analysis; AKG performed project development, data collection; VI took part in data management; MA contributed to data management; AN performed data collection, data management; AH participated in data collection, project development; SS took part in data management; HB contributed to data collection; MJS, LR, JS, MAV, LRK participated in project development.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflicts of interest.

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