Review – Kidney Cancer

Active Surveillance in Small Renal Masses in the Elderly: A Literature Review

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Abstract

Context: Small renal masses have become increasingly common due to widespread imaging; however, optimal management of these lesions in the elderly can be complex due to the competing risks of intervention, natural history of disease, patient comorbidities, and expectations. In the properly selected elderly patient, active surveillance remains an accepted and attractive treatment approach.

Objective: We completed a literature review of small renal masses (enhancing, <4 cm, T1aN0M0 disease) in the elderly, aged ≥70 yr, aimed at identifying the utility of active surveillance in this population. The primary outcomes were conversion to active treatment while on active surveillance and cancer-specific mortality. Secondary outcomes included predictors of treatment, type of treatment performed (partial nephrectomy, radical nephrectomy, and ablation), progression to metastases, all-cause mortality, tumor growth rate, and demographic data including age and Charlson Comorbidity Index.

Evidence acquisition: A comprehensive search of electronic databases (e.g., MEDLINE, EMBASE, SCOPUS, Web of Science, and the Cochrane Library) using search terms “small renal mass” OR “SRM,” AND “elderly,” “senior,” “aging,” “geriatric,” OR “octogenarian” was completed. All randomized controlled trials, nonrandomized comparison studies, and case series were included and screened by the reviewers. All comparison studies included in the systematic review were assessed for methodological quality using the Cochrane Risk of Bias tools.

Evidence synthesis: Seventeen primary studies including 36,495 patients met the inclusion criteria for the systematic review. All studies were retrospective institutional chart or the Surveillance, Epidemiology, and End Results database reviews. There was a low (4–26%) rate of conversion to active treatment for active surveillance in the identified studies over a follow-up interval of up to 91.5 mo. Overall mortality was substantial in this elderly cohort, with 15–51% of patients being deceased over the course of study follow-up; however, there was minimal cancer-specific mortality due to patients succumbing to alternative comorbid disease. In the future, patient comorbidity and biological age versus the natural history of the individualized tumor biology may play an increasing role in the discussion regarding treatment options and consideration of active surveillance.

Conclusions: Active surveillance is an effective management strategy in the elderly population. Few patients required the conversion to active treatment and there was low cancer-specific mortality. The majority of patients who expired over the course of the identified studies succumbed to alternative disease. The goal of treatment strategies should include weighing patient-specific prognosis relative to their competing health risks and treatment goals against the natural history of disease and risks of intervention.

Patient summary: In this review article, the authors examined the utility of active surveillance in the setting of a small localized renal mass in the elderly population. Despite being on surveillance, we found that cancer-specific outcomes were excellent, and overall mortality was often a result of comorbid disease. However, there is significant heterogeneity among elderly patients, and treatment approaches should be focused around patient-centered goals and prognosis.

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1. Introduction

Small renal masses (SRMs), defined as incidentally discovered enhancing renal masses <4 cm in maximal diameter with imaging consistent with T1aNOM0 disease, have become increasingly common due to widespread imaging [1,2]. Owing to the variable natural history of renal tumors based on histology and size, SRMs represent a clinically diverse spectrum of disease [3,4]. As the availability and access to renal tumor biopsy (RTB) continues to increase, improved prognostication of these lesions may also improve [5–8]. Numerous treatment approaches including extirpative surgery (ie, partial or radical nephrectomy), tissue ablation (ie, cryotherapy and radiofrequency ablation), and active surveillance have all been proved to be effective in the management of SRMs [9–13].

However, in elderly patients, the optimal management strategy can be a challenging therapeutic dilemma. This represents the competing risks of intervention versus the natural history of the disease, increased incidence of comorbid conditions (ie, cardiovascular, pulmonary, nephrological, and neurological conditions), frailty and altered physiology (ie, wound healing, Eastern Cooperative Oncology Group performance status, and mobility), medications (ie, anticoagulation and nephrotoxic medications), life expectancy, and goals of care directives within this demographic relative to their younger counterparts [14–18]. Given these additional considerations, careful review of each patient case and patient-centered discussions are critical prior to selecting a therapeutic approach.

In a significant number of cases, active surveillance remains an important therapeutic alternative within this patient population and is well accepted as an initial treatment approach in management guidelines worldwide [9,11,19,20]. We therefore aimed to evaluate the efficacy of an active surveillance approach to SRMs in the elderly by systematically reviewing the existing literature.

2. Evidence acquisition

2.1. Search methodology

A comprehensive search of electronic databases (eg, MEDLINE, EMBASE, SCOPUS, Web of Science, and the Cochrane Library) using search terms “small renal mass” OR “SRM”, AND “elderly,” “senior,” “aging,” “geriatric,” OR “octogenarian” was completed. Years of publication included studies published within the last 10 yr from July 2007 until July 2017. Conference proceedings and abstracts were also searched and reviewed, but not included in the final systematic review. All randomized controlled trials, nonrandomized comparison studies, and case series were included. All human studies that were published in English language were included. Reference lists of included studies were also checked to identify missing studies in the primary search. In the case of duplicate or overlapping study series/cohorts, the most recent publication cohort was used.

The reviewers screened abstracts, reviewed full-text versions of all studies, and classified and extracted data. All comparison studies included in the systematic review were assessed for methodological quality using the Cochrane Risk of Bias tools. Disagreements were resolved by further group review.

2.2. Assessment of study eligibility

We systematically reviewed each study according to the following criteria: (1) there were no study format restrictions for the systematic review; (2) patients had an SRM defined by the criteria listed above (enhancing, <4 cm in maximal diameter, and imaging consistent with T1aNOM0 disease; where studies included patients with larger renal masses, wherever possible, only the subset with T1aNOM0 disease was included and/or reflected in our manuscript); (3) average (mean or median) patient age was ≥70 yr and/or the study cohort contained a subset of patients ≥70 yr old (where studies included patients aged <70 yr, wherever possible, only the subset >70 yr of age was included and/or reflected in our manuscript); (4) the study enrolled at least 10 patients; (5) the study reported follow-up data on the incidence of active treatment if on surveillance or treatment comparison, cancer-specific mortality, and/or all-cause mortality; (6) the study was completed within the last 10 yr; (7) conference proceedings and abstracts were excluded; and (8) the study was published in English.

2.3. Outcomes of interest

The primary outcomes of interest were requirement for active treatment on active surveillance and cancer-specific mortality. Secondary outcomes included predictors of treatment, type of treatment performed (partial nephrectomy, radical nephrectomy, ablation), progression to metastases, all-cause mortality, tumor growth rate, and demographic data including age and Charlson Comorbidity Index. Owing to the heterogeneity of the data, a meta-analysis could not be run.

2.4. Study review

A total of 4277 studies were identified using our search criteria for screening (Fig. 1). All studies were screened based on their titles, and 113 studies were advanced to abstract screening. Once duplicates, conference proceedings and abstracts, and non-English texts were removed, 76 abstracts were reviewed according to basic data requirements applying to SRMs in the elderly and 27 proceeded to full-text review.

Of the 27 remaining for review, 10 were excluded based on failure to meet the eligibility criteria defined above. Thus, a total of 17 studies (n = 36 495 patients) were identified, which met our inclusion criteria for the systematic review (Table 1) [21–37]. All studies were retrospective institutional chart or the Surveillance, Epidemiology, and End Results (SEER) database reviews. No randomized controlled trial was included.
3. Evidence synthesis

3.1. Treatment

3.1.1. Conversion to treatment while on active surveillance

Within existing literature guidelines, active surveillance remains an important therapeutic consideration for elderly patients and can potentially defer treatment indefinitely for patients at low risk [9,11,19,20]. For patients who are elderly and may carry significant comorbidity profiles, this may be ideal to spare them the risk of complications and side effects from treatment. Despite this, a small subset of patients demonstrate higher-risk features, changing disease biology, or patient-specific concerns during the course of active surveillance and require progression into treatment.

Of the reviewed studies, four were identified to explicitly address patients converting to treatment while on surveillance protocol. The conversion rate ranged between 4% and 26% (4%, 4%, 9%, and 26%) requiring treatment over a course of 24–91.5 mo of follow-up [21,23,28,35]. This demonstrates a low rate of conversion, as reflected in Table 2, and reinforces that many elderly patients can remain on active surveillance for a prolonged period of time.

In the study by Brunocilla et al [28], the higher conversion rate (26%) likely represented an increased follow-up interval (91.5 mo). Even so, it is clear that the vast majority of patients who pursue an active surveillance treatment protocol do not end up having to undergo treatment in the short and medium term, suggesting a significant overdiagnosis of disease that may not be clinically significant during the lifetime of an elderly patient. In these cases in particular, active surveillance may be the optimal management strategy.

3.1.2. Comparison against and within treated cohorts

Furthermore, when comparing active surveillance against other management options including partial nephrectomy, radical nephrectomy, and ablation, no significant difference was noted in cancer-specific mortality in all studies except one (Table 3) [21,22,24,27,31,32]. In the largest cohort, Becker et al [27] reviewed the SEER database for 6237 patients who underwent immediate nephrectomy versus a period of surveillance followed by delayed nephrectomy (both partial and radical nephrectomy). Despite a delay of at least 3 mo with a mean of 29 mo, there was no difference in 5-yr cancer-specific mortality. Again, this suggests that active surveillance with close follow-up is a reasonable alternative in this patient demographic with little to no survival impairment. Taking into account the morbidity of intervention including the risk of postoperative complications, perioperative recovery, and renal insufficiency/impairment, this must be carefully weighed in the elderly and comorbid patients [38,39]. In the 2015 study by Russell et al [24], they demonstrated a significantly decreased hazards ratio for patients undergoing ablative therapy or partial nephrectomy versus active surveillance. However, their analysis included patients with more aggressive TNM (tumor, node, and metastasis) staging outside of the T1a SRM cohort defined by this systematic review. As a result, this finding likely reflects a selection bias within that particular study subset rather than an overall trend in the data reviewed [24].

3.1.3. Active surveillance versus watchful waiting

One key distinction within the elderly population is to identify patients who may be deemed appropriate for watchful waiting, rather than an active surveillance approach. Watchful waiting is an appropriate strategy for elderly or comorbid individuals in whom curative intervention would never be considered. This may be due to patient factors, such as comorbidities that preclude any intervention for cure, and/or goals of care and patient values. Treatment for symptomatic progression would be considered if needed. Conversely, the goal of active surveillance involves close monitoring and delayed (possibly indefinitely) treatment of the SRMs once it reaches a threshold where cure remains likely. It is important to identify this distinction, particularly within an elderly patient cohort with significant competing health risks, as failure to do so may subject a patient who is appropriate for a watchful waiting strategy to unnecessarily frequent follow-up tests despite never considering intervention for their disease.

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![Systematic review inclusion criteria.](image-url)
Table 1 – Study details and patient demographics by article.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Prospective/retrospective</th>
<th>Average age (yr)</th>
<th>Charlson Comorbidity Index</th>
<th>Sample size</th>
<th>Follow-up (mo)</th>
<th>Results:</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al [21]</td>
<td>2017</td>
<td>Retrospective institutional chart review</td>
<td>Median 82</td>
<td>2</td>
<td>59</td>
<td>51</td>
<td>4% of patients in active surveillance arm underwent treatment; 33–48% of patients deceased, with no difference in overall survival or cancer-specific mortality between partial/radical nephrectomy, ablation, and active surveillance (only age predicted overall survival); 3% progressed to metastases</td>
<td></td>
</tr>
<tr>
<td>An et al [22]*</td>
<td>2017</td>
<td>Retrospective institutional chart review</td>
<td>Mean 70.9</td>
<td>1</td>
<td>319</td>
<td>36</td>
<td>All patients underwent nephrectomy (partial vs radical), no difference in 5-yr cancer-specific or overall survival</td>
<td>Included patients with larger tumors in result analysis</td>
</tr>
<tr>
<td>Celtik et al [23]*</td>
<td>2017</td>
<td>Retrospective institutional chart review</td>
<td>Median 83.4</td>
<td>2</td>
<td>78</td>
<td>39.9</td>
<td>All patients started on active surveillance, 0.2 cm mean growth rate, 8% underwent treatment, 15% deceased, with 3% progressing to metastases and cancer specific mortality at end of follow-up</td>
<td>Included patients with tumors up to 7 cm in result analysis</td>
</tr>
<tr>
<td>Russell et al [24]</td>
<td>2015</td>
<td>Retrospective SEER database review</td>
<td>Mean 82</td>
<td>Not published</td>
<td>1719</td>
<td>43</td>
<td>Cancer-specific mortality HR 0.39 comparing ablation/partial nephrectomy versus active surveillance, but not significant in simple/radical nephrectomy versus active surveillance, and increased non-cancer-related mortality in active surveillance group at the end of follow-up</td>
<td></td>
</tr>
<tr>
<td>Tan et al [25]*</td>
<td>2015</td>
<td>Retrospective SEER database review</td>
<td>Subgroup 65–74</td>
<td>Not published</td>
<td>10 466</td>
<td>Not published</td>
<td>1.6× greater probability of nonoperative management, 1.5× greater probability of ablation compared with 55–64</td>
<td></td>
</tr>
<tr>
<td>Miller et al [26]</td>
<td>2015</td>
<td>Retrospective institutional chart review</td>
<td>Mean 84</td>
<td>2.1</td>
<td>95</td>
<td>34.8</td>
<td>All patients treated with cryoablation or radiofrequency ablation, 36% of patients deceased at 3.7 yr; progression-free survival at 1 yr was 99%; 3 yr 97%, and 5 yr 97%; overall survival at 1 yr was 98%, 3 yr 83%, and 5 yr 61%, with only one patient succumbing to metastatic disease</td>
<td>Biopsy-proven sporadic RCC subgroup had increased 5-yr cancer-specific mortality, 13% complication rate (5% Clavien III or higher)</td>
</tr>
<tr>
<td>Becker et al [27]</td>
<td>2014</td>
<td>Retrospective SEER database review</td>
<td>Mean 74</td>
<td>2.1</td>
<td>6237</td>
<td>Not published</td>
<td>All patients underwent nephrectomy (partial vs radical), but delayed (&gt;3 mo, mean 29 mo) versus immediate with no difference in 5-yr cancer-specific mortality</td>
<td></td>
</tr>
<tr>
<td>Brunocilla et al [28]</td>
<td>2014</td>
<td>Retrospective institutional chart review</td>
<td>Mean 75</td>
<td>3</td>
<td>58</td>
<td>91.5</td>
<td>All patients started on active surveillance, 0.4 cm mean growth rate, 26% underwent treatment, 43% of patients deceased in active surveillance, with 3% progressing to metastases and cancer-specific mortality at the end of follow-up</td>
<td>Predictors were faster, linear, and volumetric growth rates for treatment</td>
</tr>
<tr>
<td>Patel et al [37]*</td>
<td>2014</td>
<td>Retrospective SEER database review</td>
<td>Subgroup 75–80</td>
<td>Not published</td>
<td>1838</td>
<td>Not published</td>
<td>Noted decreased HRs for overall survival (HR 0.33–0.38) and cancer-specific survival (HR 0.27–0.40) for treatment groups versus nonsurgical management groups</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Year of publication</td>
<td>Prospective/retrospective</td>
<td>Average age (yr)</td>
<td>Charlson Comorbidity Index</td>
<td>Sample size</td>
<td>Follow-up (mo)</td>
<td>Results: Additional comments</td>
<td></td>
</tr>
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<td>-------------------------</td>
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<td>---------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Subgroup ≥ 80</td>
<td>Not published</td>
<td>1398</td>
<td>Not published</td>
<td></td>
<td></td>
<td></td>
<td>Noted decreased HRs for overall survival (HR 0.36–0.55) and cancer-specific survival (HR 0.41–0.68) for treatment groups versus nonsurgical management group</td>
<td></td>
</tr>
<tr>
<td>Sun et al [36]*</td>
<td>2014</td>
<td>Retrospective SEER database review</td>
<td>Subgroup ≥ 75</td>
<td>Not stratified based on subgroup</td>
<td>2873</td>
<td>96.6</td>
<td>Once adjusted, patients with T1a disease and ≥75 yr of age demonstrated no significant difference in cancer-specific mortality, but worse other-cause mortality in the partial/radical nephrectomy versus nonsurgical management group (HR 0.47–0.56)</td>
<td></td>
</tr>
<tr>
<td>Hillyer et al [29]*</td>
<td>2012</td>
<td>Retrospective institutional chart review</td>
<td>Mean 74.5</td>
<td>1</td>
<td>20</td>
<td>9.5</td>
<td>All patients underwent robotic partial nephrectomy, no difference compared with younger patients in peri- and postoperative complications, 8% of patients deceased, with 0% cancer-specific mortality at the end of follow-up</td>
<td></td>
</tr>
<tr>
<td>Kates et al [30]</td>
<td>2011</td>
<td>Retrospective SEER database review</td>
<td>Mean 79</td>
<td>Not published</td>
<td>2733</td>
<td>Not published</td>
<td>Elderly patients were more likely to undergo radical nephrectomy versus partial nephrectomy compared with their younger counterparts</td>
<td>Included patients with larger tumors in result analysis</td>
</tr>
<tr>
<td>Lane et al [31]*</td>
<td>2010</td>
<td>Retrospective institutional chart review</td>
<td>Median 79</td>
<td>1</td>
<td>378</td>
<td>46.8</td>
<td>28% of patients deceased, with 4% cancer-specific mortality at the end of follow-up, no difference between radical nephrectomy, nephron sparing intervention, or active surveillance (only age and Charlson Comorbidity Index predicted all-cause mortality); additional 1% patients were alive but with distant metastases</td>
<td></td>
</tr>
<tr>
<td>Deklaj et al [32]</td>
<td>2010</td>
<td>Retrospective institutional chart review</td>
<td>Mean 75.7</td>
<td>Not published</td>
<td>66</td>
<td>21</td>
<td>All patients underwent treatment (laparoscopic radical nephrectomy, partial nephrectomy vs ablation), with decreased CrCl and increased stage 3 CKD in radical nephrectomy group; no reported difference in metastatic progression between groups</td>
<td></td>
</tr>
<tr>
<td>Beisland et al [33]</td>
<td>2009</td>
<td>Retrospective institutional chart review</td>
<td>Mean 76.6</td>
<td>Not published</td>
<td>35</td>
<td>33</td>
<td>All patients started on active surveillance, 51% of patients deceased, with 0% 5-yr cancer-specific mortality; no patients within the T1a cohort developed metastases</td>
<td></td>
</tr>
<tr>
<td>O’Connor et al [34]</td>
<td>2009</td>
<td>Retrospective institutional chart review</td>
<td>Mean 77</td>
<td>3</td>
<td>13</td>
<td>20.9</td>
<td>All patients started on active surveillance, 42% of patients deceased, with 0% cancer-specific mortality in the SRM group at the end of follow-up; no patients within the T1a cohort developed metastases</td>
<td></td>
</tr>
<tr>
<td>Abouassaly et al [35]</td>
<td>2008</td>
<td>Retrospective institutional chart review</td>
<td>Median 81</td>
<td>2</td>
<td>110</td>
<td>24</td>
<td>All patients started on active surveillance; 0.3 cm mean growth rate, 4% underwent treatment, 31% of patients deceased, with 0% cancer-specific mortality at the end of follow-up; no progression to metastases was reported</td>
<td></td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; HR = hazard ratio; RCC = renal cell carcinoma; SEER = Surveillance, Epidemiology, and End Results; SRM = small renal mass.

*Sample size used for analysis only if subgroup contained elderly patients with T1a small renal masses where possible.
Table 2 – Conversion to treatment while on active surveillance.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Average age (yr)</th>
<th>Charlson Comorbidity Index</th>
<th>Sample size</th>
<th>Follow-up (mo)</th>
<th>Results (truncated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al [21]</td>
<td>2017</td>
<td>82</td>
<td>2</td>
<td>59</td>
<td>51</td>
<td>4% of patients in active surveillance arm underwent treatment</td>
</tr>
<tr>
<td>Celnik et al [23]</td>
<td>2017</td>
<td>83</td>
<td>2</td>
<td>78</td>
<td>39.9</td>
<td>All patients started on active surveillance, 9% underwent treatment</td>
</tr>
<tr>
<td>Brunocilla et al [28]</td>
<td>2014</td>
<td>75</td>
<td>3</td>
<td>58</td>
<td>91.5</td>
<td>All patients started on active surveillance, 26% underwent treatment</td>
</tr>
<tr>
<td>Aboussaly et al [35]</td>
<td>2008</td>
<td>81</td>
<td>2</td>
<td>110</td>
<td>24</td>
<td>All patients started on active surveillance, 4% underwent treatment</td>
</tr>
</tbody>
</table>

Table 3 – Comparison of treatment outcomes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Average age (yr)</th>
<th>Charlson Comorbidity Index</th>
<th>Sample size</th>
<th>Follow-up (mo)</th>
<th>Treatment groups</th>
<th>Results (truncated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al [21]</td>
<td>2017</td>
<td>82</td>
<td>2</td>
<td>59</td>
<td>51</td>
<td>Partial and radical nephrectomy, ablation, active surveillance</td>
<td>No difference in overall survival or cancer-specific mortality between partial.radical nephrectomy, ablation, and active surveillance (only age predicted overall survival)</td>
</tr>
<tr>
<td>An et al [22]</td>
<td>2017</td>
<td>70.9</td>
<td>1</td>
<td>319</td>
<td>36</td>
<td>Partial versus radical nephrectomy</td>
<td>No difference in 5-yr cancer-specific or overall survival</td>
</tr>
<tr>
<td>Russell et al [24]</td>
<td>2015</td>
<td>82</td>
<td>Not published</td>
<td>1719</td>
<td>43</td>
<td>Partial and radical nephrectomy, ablation, active surveillance</td>
<td>Cancer-specific mortality HR 0.39 comparing ablation/partial nephrectomy versus active surveillance, but not significant in simple/radical nephrectomy versus active surveillance, and increased non-cancer-related mortality in active surveillance group at the end of follow-up</td>
</tr>
<tr>
<td>Becker et al [27]</td>
<td>2014</td>
<td>74</td>
<td>2.1</td>
<td>6237</td>
<td>Not published</td>
<td>Nephrectomy versus delayed nephrectomy</td>
<td>All patients underwent nephrectomy (partial vs radical), but delayed (&gt;3 mo, mean 25 mo) versus immediate with no difference in 5-yr cancer-specific mortality</td>
</tr>
<tr>
<td>Lane et al [31]</td>
<td>2010</td>
<td>79</td>
<td>1</td>
<td>378</td>
<td>46.8</td>
<td>Radical nephrectomy, nephron sparing, active surveillance</td>
<td>No difference between radical nephrectomy, nephron sparing intervention, and active surveillance (only age and Charlson Comorbidity Index predicted all-cause mortality)</td>
</tr>
<tr>
<td>Deklaj et al [32]</td>
<td>2010</td>
<td>75.7</td>
<td>Not published</td>
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<td>21</td>
<td>Partial and radical nephrectomy, ablation</td>
<td>All patients underwent treatment (laparoscopic radical nephrectomy, partial nephrectomy vs ablation), with decreased CrCl and increased stage 3 CKD in radical nephrectomy group</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; HR = hazard ratio.

3.2. Survival

3.2.1. Overall survival, cancer-specific mortality, and progression to metastases

Owing to the presence of significant comorbidities within the elderly population demographic, a substantial proportion of patients were deceased during the course of study follow-up. In the reviewed studies (excluding follow-up of <1 yr), 15%, 28%, 31%, 36%, 42%, 43%, 33–48%, and 51% of patients were deceased at the end of 39.3, 46.8, 24, 34.8, 20.9, 91.5, 51, and 33 mo of follow-up, respectively [21,23,26,28,31,33–35]. This is summarized in Table 4 and is in concordance with previously published studies: Hollingsworth et al [40] demonstrated that the competing risk mortality within 5 yr was 28.2% in patients over 70 yr old, regardless of the renal tumor. In spite of a mortality rate approaching one-third to one-half of study patients, most studies reported cancer-specific mortality or progression to metastases of <5% (0–5%) during follow-up, and this did not differ between treatment groups and active surveillance cohorts. These findings are consistent with the literature results recently published from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry: patients selecting active surveillance versus primary intervention were found to have no difference in cancer-specific mortality or overall survival at 5 yr of follow-up [41]. Again, this reinforces that many patients succumb to other comorbid diseases rather than their renal cancer and that there may be an appropriate window to pursue active surveillance in the elderly population.

However, two SEER database reviews by Patel et al [37] and Sun et al [36] in 2014 demonstrated an increase in other-cause mortality in the nonsurgical management group versus partial and radical nephrectomy, in addition to 5-yr cancer-specific mortality of 10.6% in the surveillance arm. Compared with other contemporary studies, these reported data are higher and may represent a byproduct of using administrative data. As Smallbone et al [42] presented in 2014, claims data collected in observational analyses and database review allow for the identification of "nonsurgical management," but often does not have the granularity to distinguish whether these patients are...
Table 4 – Overall survival and cancer-specific survival.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Average age (yr)</th>
<th>Charlson Comorbidity Index</th>
<th>Sample size</th>
<th>Follow-up (mo)</th>
<th>Treatment groups</th>
<th>Results (truncated)</th>
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<tbody>
<tr>
<td>Tang et al [21]</td>
<td>2017</td>
<td>82</td>
<td>2</td>
<td>59</td>
<td>51</td>
<td>Partial and radical nephrectomy, ablation, active surveillance</td>
<td>33–48% of patients deceased, with no difference in overall survival or cancer-specific mortality between partial/radical nephrectomy, ablation, and active surveillance (only age predicted overall survival)</td>
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<tr>
<td>Celtik et al [23]</td>
<td>2017</td>
<td>83</td>
<td>2</td>
<td>78</td>
<td>39.9</td>
<td>Active surveillance</td>
<td>15% of patients deceased, with 3% cancer-specific mortality at the end of follow-up</td>
</tr>
<tr>
<td>Miller et al [26]</td>
<td>2015</td>
<td>84</td>
<td>2.1</td>
<td>95</td>
<td>34.8</td>
<td>Cryoablation, Radiofrequency ablation</td>
<td>36% of patients deceased at 3.7 yr, progression-free survival at 1 yr was 99%, 3 yr 97%, 5 yr 97%</td>
</tr>
<tr>
<td>Brunocilla et al [28]</td>
<td>2014</td>
<td>75</td>
<td>3</td>
<td>58</td>
<td>91.5</td>
<td>Active surveillance</td>
<td>43% of patients deceased in active surveillance, with 3% cancer-specific mortality at the end of follow-up</td>
</tr>
<tr>
<td>Patel et al [37]</td>
<td>2014</td>
<td>Subgroup 75–80</td>
<td>Not published</td>
<td>1838</td>
<td>Not published</td>
<td>Nonsurgical management, partial and radical nephrectomy</td>
<td>Noted decreased HRs for overall survival (HR 0.33–0.38) and cancer-specific survival (HR 0.27–0.40) for treatment groups versus nonsurgical management group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subgroup ≥80</td>
<td>Not published</td>
<td>1398</td>
<td>Not published</td>
<td>Nonsurgical management, partial and radical nephrectomy</td>
<td>Noted decreased HRs for overall survival (HR 0.36–0.55) and cancer-specific survival (HR 0.41–0.68) for treatment groups versus nonsurgical management group</td>
</tr>
<tr>
<td>Sun et al [36]</td>
<td>2014</td>
<td>Subgroup ≥75</td>
<td>Not stratified based on subgroup</td>
<td>2873</td>
<td>96.6</td>
<td>Nonsurgical management, partial and radical nephrectomy</td>
<td>Once adjusted, patients with T1a disease and ≥75 yr of age demonstrated no significant difference in cancer-specific mortality, but worse other-cause mortality in the partial/radical nephrectomy group versus nonsurgical management group (HR 0.47–0.56)</td>
</tr>
<tr>
<td>Lane et al [31]</td>
<td>2010</td>
<td>79</td>
<td>1</td>
<td>378</td>
<td>46.8</td>
<td>Radical nephrectomy, nephron sparing, active surveillance</td>
<td>28% of patients deceased, with 4% cancer-specific mortality at the end of follow-up: no difference between radical nephrectomy, nephron sparing intervention, and active surveillance (only age and Charlson Comorbidity Index predicted all-cause mortality)</td>
</tr>
<tr>
<td>Beisland et al [33]</td>
<td>2009</td>
<td>76.6</td>
<td>Not published</td>
<td>35</td>
<td>33</td>
<td>Active surveillance</td>
<td>51% of patients deceased, with 0% 5-yr cancer-specific mortality</td>
</tr>
<tr>
<td>O’Connor et al [34]</td>
<td>2009</td>
<td>77</td>
<td>3</td>
<td>13</td>
<td>20.9</td>
<td>Active surveillance</td>
<td>42% of patients deceased, with 0% cancer-specific mortality at the end of follow-up</td>
</tr>
<tr>
<td>Abouassaly et al [35]</td>
<td>2008</td>
<td>81</td>
<td>2</td>
<td>110</td>
<td>24</td>
<td>Active surveillance</td>
<td>31% of patients deceased, with 0% cancer-specific mortality at the end of follow-up</td>
</tr>
</tbody>
</table>

HR = hazard ratio.
undergoing watchful waiting or active surveillance. In their surveillance cohort, once additional criteria (eg, imaging and hospice claims) were applied, the differences in cancer-specific and overall mortality were no longer significant against a treated comparison group.

To further delineate this competing risk, Kutikov et al [43] developed and validated a competing risk nomogram that identified renal cancer–specific mortality, non–renal cancer–specific mortality, and non–cancer–related mortality. For example, a 75-yr-old Caucasian male with a 3 cm renal tumor would have 4% mortality from renal cancer, 5% mortality from other cancer, and 15% mortality from non–cancer-related causes. Similarly, in a decision analysis, Abouassaly et al [44] found an average age threshold of 74 yr, after which active surveillance was preferred and the risk of systemic recurrence was <1.3%/yr. Development of competing health risk assessment tools, such as these nomograms, will be imperative to informing and counseling patients prior to pursuing therapy in this demographic.

3.2.2. Disease biology, natural history, progression, and surveillance

The natural history of SRMs has been extensively reviewed in the literature [1,3,4,5,6]. Of incidentally presenting SRMs <4 cm, approximately 23% are benign and 77% are malignant [47,48]. Lesions may range from those with benign histologies including oncocytomas, metanephric adenomas, and angiomylipomas to indolent lesions including papillary type 1 renal cell carcinoma, to more aggressive malignant histological variants to rare cases of lymphoma, sarcoma, and metastases [9]. Despite this range in histology, the ability to accurately distinguish between variant histology based on radiographic markers remains limited. Several studies have evaluated the degree of hyper-/hypovascularity, enhancement patterns, hemorrhage, calcifications, necrosis, and pseudocapsules, but have not identified any definitive radiographic predictors of benign versus malignant disease, particularly within SRMs [49–53].

Ultimately, with an active surveillance approach, the goal is to tailor enrolment and follow-up based on the metastatic potential, and intervene if accelerated growth occurs and the patient is well enough to undergo treatment [54]. However, the potential for widely disparate histology despite similar radiographic presentation and the lack of histology-specific surveillance research continue to limit the development of an optimal surveillance strategy and risk stratification for these individuals.

In the majority, however, SRMs have been shown to have slow growth rates: contemporary literature suggests a growth rate of approximately 0.12–0.28 cm/yr (calculated as the change in diameter or the cube root of the volumetric change) [3,46]. Furthermore, in a pooled analysis by Small et al [10] analyzing 936 masses, a considerable amount (28%) of SRMs remained stable and exhibited zero growth over the period of 3 yr. In addition to slow growth rates, these lesions tend to harbor low metastatic potential and progression. In a study by Chawla et al [3], at a mean follow-up interval of 34 mo, only 1% (3/286) of lesions progressed to metastatic disease in untreated solid renal masses, which has been consistent across most documented studies in the literature.

Given this, it remains difficult to determine a precise cutoff point for disease progression due to disparate courses of natural history and histology, as well as the limitations of using retrospective data found in the primary studies. As a result, within the reference studies, there were limited guidance and considerable variability in the definitions; however, most studies have proposed that increased growth rates (highly variable and often similar between benign and malignant groups, although generally >0.5 cm/cm yr), absolute size to >3–4 cm, development of metastases, patient acceptability/tolerability of the active surveillance regimen, and patient–surgeon discretion should be involved in the decision-making process [21,23,24,27,28,33,35,55–57]. Once factored together, a patient-centered decision can then be made, accounting for the patient’s specific disease trajectory, comorbid risk profile, lifestyle, and values.

Further, a surveillance strategy also faces similar challenges: differing histology and disease biology make it difficult to suggest a broader surveillance strategy. Surveillance follow-up schedules should be based on malignancy/indolence, and further research is required to tailor histology-specific surveillance. For example, an oncocytoma or fat-poor AML could more appropriately undergo a less intense surveillance regimen. However, broadly within the studies reviewed by this paper and our experience, we found that most clinicians are repeating cross-sectional imaging at least once within the first 6 mo and then every 6 mo to 1 yr thereafter [21,27,28,31,33–35,58]. Although most studies used CT for their follow-up, ultrasound and magnetic imaging studies remain a possibility if accessible. Importantly, a physical examination, bloodwork (complete blood count, electrolytes, creatinine, and urinalysis), and chest imaging should not be omitted [58]. Similarly, these findings echo the surveillance strategy used by the DISSRM group recently published in the Journal of Urology [57].

Overall, a hypothetical elderly patient presenting with a 2 cm mass growing at a rate of up to 0.3 cm/yr would take 6–7 yr to reach 4 cm with limited metastatic potential. Particularly in the case of an elderly patient with comorbidities and limited life expectancy, the SRM may likely never become life limiting; due to a low progression rate, cancer-specific mortality is rare while the complications of treatment increase, and highlights the necessary nuance when carefully selecting a treatment strategy and in discussion with patients. We have included a proposed management algorithm for practicing urologists to guide their approach to SRMs in Figure 2.

3.2.3. Patient heterogeneity

However, further stratification in addition to chronological age is required. Progressively, patients in the industrialized world are living longer. Although partly this has shifted from years of life lost (due to premature mortality) to years lived with disability, the overall disability adjusted life years and healthy life expectancy have both increased with modern medicine and improvements in prevention and treatment of cardiovascular disease, malignancy, and
Patient is an appropriate candidate for active surveillance

Exclusion:
- Does not align with a patient’s goals of care, preference, and/or acceptability of treatment
- Candidate for watchful waiting
- Patient unable to complete follow-up
- Does not meet TlAJNOMD
- Surgeon discretion

Patient on active surveillance

Surveillance protocol:
- Repeat cross-sectional imaging at 6 mo, then 6–12 mo thereafter (ultrasound/MRI if available may be used at surgeon discretion)
- Physical examination
- Bloodwork (CBC, electrolytes, creatinine, urinalysis)
- Chest imaging
- ≤Biopsy (controversial)

Patient progression:
- Increased growth rates (>0.5 cm/yr)
- Absolute size (>3–4 cm)
- Development of metastases
- Patient acceptability/tolerability of the active surveillance regimen
- Patient-surgeon discretion

Fig. 2 – Proposed treatment algorithm. CBC = complete blood count; MRI = magnetic resonance imaging.

infection [59]. However, as patients live longer, they represent a heterogeneous cohort with broadly differential functional status, physical well-being/frailty, socioeconomic status, and access to health care. In response, online calculators available at ePrognosis (www.epronostics.com) have attempted to use combined comorbidity scores to further stratify patients, measure frailty, and improve on life expectancy calculations, which may be critical when informing patients and personalizing their surveillance strategy [60].

Manton and Vaupel [61] demonstrated widely differing survival and life expectancy for patients at the age of 80 yr based on location. Compared across the USA, Japan, Sweden, France, and England in 1987, life expectancy at age 80 yr in the USA was 9.1 more years for a Caucasian female (compared with 8.5, 8.3, 8.6, and 8.1 yr, respectively) and 7.0 more years for a Caucasian male (6.9, 6.5, 6.7, and 6.2 yr, respectively) [61]. Biological age and the accumulation of comorbidities or lack thereof (ie, Charlson Comorbidity Index) can often further inform individualized patient discussion regarding future potential prognosis, goals of care, and preferences concerning treatment decisions. For example, Cho et al [62] demonstrated that for a patient aged 75 yr, a male individual’s life expectancy was 12.7 yr with no comorbidities versus 7.4 yr in the high-comorbidity subgroup, and a female individual’s life expectancy would be 15.3 yr with no comorbidities versus 8.5 yr in the high-comorbidity subgroup.

Similarly, the Tayside Active Surveillance Cohort study on SRMs again demonstrated significantly disparate survival curves based on comorbidity [63]. The study found 4% progression to metastases and cancer-specific mortality versus 21% mortality from non–cancer-related causes (hazard ratio 1.142/comorbidity), highlighting the clinical importance of assessing patients based on comorbid status. Thus, biological age, as compared with chronological age, can also further predict life expectancy when reviewing the appropriateness of an active surveillance strategy.

3.2.4. Future considerations: RTB

RTB continues to play an increasing role in the management of SRMs but remains a controversial issue. In particular, RTB may be able to better identify patients who are candidates for active surveillance versus treatment with extirpative ablative therapy [48]. In a biopsy algorithm by Rahbar et al [64] for patients who had undergone robotic partial nephrectomy for SRMs, 23.9% of patients were assigned to active surveillance due to tumor pathology and comorbidities, demonstrating a theoretical reduction in the number of unnecessary surgeries and resultant harm to these patients if RTB had been completed. With this in mind, large retrospective studies have further demonstrated a diagnostic rate of around 80–90% and benign pathology is revealed in one in four biopsies [6,7]. If one were contemplating watchful waiting, a biopsy could be omitted given that the only benefit may be a benign histology that would require no follow-up whatsoever.

Within our experience at our center, we are in favor of performing biopsies where the results of the biopsy may change management for the patient. In particular, when intervention is being considered or in high-risk patients (comorbidities, marginal renal function, solitary kidney, and multiple masses), these cases present optimal opportunities for the consideration of RTB. However, accessibility, accuracy, and complication rates still remain variable and pose a challenge to widespread adoption of RTB.

We additionally recognize that the only way to move forward within our understanding of renal masses and their differing presentation is to better understand tumor histology and malignant potential, and improve diagnostic rates, such that we can offer personalized surveillance or treatment strategies to patients. This remains a liberal indication and requires further refinement in future research.

3.3. Limitations of the study

Our systematic review was limited by the quality and quantity of primary studies within this field. In aggregate, there were a limited number of primary studies (n = 17). In addition to few primary studies, there was significant heterogeneity in the definitions between study end points, study population and demographics, patient selection, and treatment options, restricting the conclusions of our systematic review and their applicability. Furthermore, limited long-term data (only one study with follow-up data
past 5 yr) and no meta-analytic data have been published to report on the long-term relative safety of active surveillance. A meta-analysis could not be run within our review, and there was no controlled trial within the reviewed literature.

Finally, one limitation of the primary studies highlighted above remains a difficulty in differentiating patients with active surveillance versus watchful waiting using administrative data only. Within the listed and future primary studies, further scrutiny to adequately assess patients undergoing active surveillance is required.

3.4. Future research

The field of SRMs continues to evolve and requires further research. In particular, we believe that the greatest area for potential benefit is in further histology-specific data. As opposed to grouped SRM cohorts, these will be invaluable to an increased understanding of how differing renal tumor biologies behave. These nuances will then allow clinicians to ascertain ideal surveillance and treatment strategies, and cutoffs for progression to tailor them to their patients and individual risk profiles. In this light, RTB continues to play an important role: increasing the identification and risk stratification of high- and low-risk tumor phenotypes and their natural history. We will rely on tissue until a “liquid biopsy” is available. Further long-term data and prospective trials continue to be lacking in the literature, and constitute a target for future research.

4. Conclusions

Despite limited literature existing on this topic, our systematic review findings demonstrated that there was a low rate of conversion from patients on an active surveillance strategy to treatment with partial/radical nephrectomy or ablation, and no difference in cancer-specific mortality among treated groups. Similarly, overall mortality was rarely a result of cancer-specific mortality as opposed to comorbid disease, as reflected by the published literature regarding the natural history of SRMs. Given the diverse and heterogeneous cohort of elderly patients, active surveillance remains a good option for these patients, but should be tailored to their individual prognoses and treatment goals. Further studies including large-scale prospective cohorts or randomized controlled trials are needed to fully evaluate active surveillance, and ablative and extirpative management of SRMs in the elderly.

Author contributions: Douglas C. Cheung had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Finelli, Cheung.

Acquisition of data: Finelli, Cheung.

Analysis and interpretation of data: Finelli, Cheung.

Drafting of the manuscript: Finelli, Cheung.

Critical revision of the manuscript for important intellectual content: Finelli, Cheung.

Statistical analysis: Finelli, Cheung.

Obtaining funding: None.

Administrative, technical, or material support: Finelli, Cheung.

Supervision: Finelli.

Other: None.

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References


[38] Lane BR, Gill IS. 5-Year outcomes of laparoscopic partial nephrectomy. J Urol 2007;177:70–4, discussion 4.


