Renal Functional Outcomes after Surgery, Ablation, and Active Surveillance of Localized Renal Tumors: A Systematic Review and Meta-Analysis

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Abstract

Background and objectives Management strategies for localized renal masses suspicious for renal cell carcinoma include radical nephrectomy, partial nephrectomy, thermal ablation, and active surveillance. Given favorable survival outcomes across strategies, renal preservation is often of paramount concern. To inform clinical decision making, we performed a systematic review and meta-analysis of studies comparing renal functional outcomes for radical nephrectomy, partial nephrectomy, thermal ablation, and active surveillance.

Design, settings, participants, & measurements We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from January 1, 1997 to May 1, 2015 to identify comparative studies reporting renal functional outcomes. Meta-analyses were performed for change in eGFR, incidence of CKD, and AKI.

Results We found 58 articles reporting on relevant renal functional outcomes. Meta-analyses showed that final eGFR fell 10.5 ml/min per 1.73 m² lower for radical nephrectomy compared with partial nephrectomy and indicated higher risk of CKD stage 3 or worse (relative risk, 2.56; 95% confidence interval, 1.97 to 3.32) and ESRD for radical nephrectomy compared with partial nephrectomy. Overall risk of AKI was similar for radical nephrectomy and partial nephrectomy, but studies suggested higher risk for radical nephrectomy among T1a tumors (relative risk, 1.37; 95% confidence interval, 1.13 to 1.66). In general, similar findings of worse renal function for radical nephrectomy compared with thermal ablation and active surveillance were observed. No differences in renal functional outcomes were observed for partial nephrectomy versus thermal ablation. The overall rate of ESRD was low among all management strategies (0.4%–2.8%).

Conclusions Renal functional implications varied across management strategies for localized renal masses, with worse postoperative renal function for patients undergoing radical nephrectomy compared with other strategies and similar outcomes for partial nephrectomy and thermal ablation. Further attention is needed to quantify the changes in renal function associated with active surveillance and nephron-sparing approaches for patients with preexisting CKD.


Introduction

The incidence of renal masses suspicious for localized kidney cancer has been increasing for several decades, possibly due to incidental diagnoses from increased use of cross-sectional imaging (1). Although kidney cancer can be aggressive, with over 14,000 deaths expected in the United States in 2016, the majority of the 60,000 newly diagnosed patients will have localized disease with favorable survival after treatment (2).

A number of management options are available for clinically localized renal masses, including surgery with partial nephrectomy (PN) or radical nephrectomy (RN), thermal ablation (TA), and active surveillance (AS). Guidelines from the American Urological Association (AUA) recommend surgery (either PN or RN) as standard of care for small renal masses (≤4 cm; clinical stage T1a) but also recommend TA and AS as acceptable approaches depending on patient comorbidities and preferences (3). For larger tumors, TA and AS are generally considered options, whereas surgery is currently the mainstay of treatment. PN is less preferred for clinical T2 tumors (>7 cm), although the current guidelines do not specifically cover this category.

Given the favorable overall and cancer-specific survival outcomes across management strategies, renal preservation is often of paramount concern (4). Except in patients with a solitary kidney, the comparative implications of each management strategy remain uncertain. The AUA, the European Association of Urology, and the National Comprehensive Cancer Network do not strictly define preference for management strategy on the basis of implications for renal function, but there has been a growing preference for PN for T1a tumors.
The focus on absolute creatinine values, lack of studies on eGFR, and absence of any randomized trials were major limitations of the literature at the time of the last AUA guidelines in 2009 (3).

Since then, a number of comparative cohort studies have been reported, and a single randomized trial evaluated renal functional outcomes of PN and RN with median follow-up of 6.7 years. The randomized trial showed decreased incidence of moderate CKD but similar rates of ESRD for PN compared with RN (6). To summarize the robust but heterogeneous literature and inform clinical decision making, we performed a systematic review and meta-analysis of studies comparing renal functional outcomes for the four major management strategies for localized renal masses suspicious for renal cell carcinoma.

Materials and Methods

Data Search Strategy

As part of efforts by the Agency for Health Research and Quality (AHRQ) to inform health care decisions through comparative effectiveness research and reviews, key informants provided input as we refined questions, established eligibility criteria, and developed a protocol (PROSPERO registration CRD42015015878) for the systematic review. We report here renal function-specific results from a broader systematic review (7). MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from January 1, 1997 (the year that the tumor, node, and metastasis Classification of Malignant Tumor staging system for renal cell carcinoma was modified and distinctions of T1a/T1b and T2a/T2b were created) to May 1, 2015. Clinical stage definitions were defined by the American Joint Committee on Cancer: T1a, ≤4 cm; T1b, >4 to ≤7 cm; T2a, >7 to ≤10 cm; T2b, >10 cm; node negative; and no evidence of distant metastases. Clinicaltrials.gov was searched for relevant studies, and information was requested from device manufacturers.

Study Selection, Data Extraction, and Quality Assessment

DistillerSR (Evidence Partners, 2010) was used to manage the screening process. Paired investigators independently screened articles to assess eligibility on the basis of predefined criteria in a Population, Intervention, Comparison, Outcome, Time framework (Supplemental Appendix) to identify comparative studies of the management options or single cohort studies of AS (given the expectation that comparative studies of AS would be sparse). The key questions included determining the comparative renal functional outcomes of different interventions for the management of a renal mass suspicious for localized renal cell carcinoma and whether these relationships differed on the basis of patient demographics, clinical characteristics, or disease severity.

Data were abstracted from studies sequentially, and paired investigators independently assessed risk of bias for individual studies. To assess risk of bias for randomized trials, the Cochrane Collaboration’s tool was used, whereas the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions was used for nonrandomized studies (8,9). Differences between reviewers were resolved through consensus. The draft AHRQ evidence report was peer reviewed and posted for public comments, which were compiled and addressed.

Data Synthesis and Analyses

All studies were summarized qualitatively. Renal functional outcomes were categorized broadly into continuous (changes in serum creatinine or eGFR largely on the basis of the Modification of Diet in Renal Disease Study equation when specified) and categorical (incidence of CKD stages ≥3, ≥3b, and ≥4 and ESRD) outcomes. Time points for outcomes vary across studies, but when possible, we used outcomes assessed via tabulated data or Kaplan–Meier curves closest to 1 year to avoid including competing causes of CKD other than the management strategy. eGFR at last follow-up was also routinely recorded. AKI was categorized as a harm rather than a primary renal functional outcome, but it is included in this report. Definitions for AKI varied across studies. Meta-analyses were conducted to reflect the authors’ definition of AKI from each study.

We conducted meta-analyses using a random effects model with the DerSimonian and Laird method when there were at least two sufficiently homogeneous studies. We identified substantial statistical heterogeneity (I² statistic >50%). Funnel plots assessed potential publication bias for categorical outcomes. All meta-analyses were conducted using STATA 12.1 (College Station, TX). Strength of evidence was graded for each category of outcomes using the scheme recommended by the AHRQ’s Methods Guide for Conducting Comparative Effectiveness Reviews, which includes evaluating reporting bias, directness of the outcome, consistency of findings, and precision of the effect estimates (10).

Results

A total of 20,829 unique citations were identified, with 13,912 excluded during abstract screening, 1028 excluded during full-text screening, and 1190 excluded during key question applicability screening (Figure 1). Overall, 147 studies reported in 150 articles were included in the broader review, with a total of 53 studies reported in 54 articles (17,784 patients) related to primary renal functional outcomes and 17 related to AKI ultimately included in this systematic review (58 total unique articles) (6,11–67). Full details of the studies can be found in the full AHRQ report (7). Only one study, reported in two articles, was a randomized trial, and the remainder were comparative cohort studies (6,11).

RN versus PN

Continuous Outcomes. A total of 34 studies assessed continuous renal functional outcomes for RN versus PN (6,11–43). In general, final compiled continuous changes in creatinine and eGFR revealed more evidence of kidney dysfunction for RN compared with PN (Table 1). The final eGFR fell a median of 15 ml/min per 1.73 m² lower with RN than with PN (~22.4 versus ~7.4 ml/min per 1.73 m²). Meta-analyses showed that the mean increase in creatinine was 0.35 mg/dl (95% confidence interval [95% CI], 0.29 to 0.41) higher and that mean decrease in eGFR was
10.5 ml/min per 1.73 m² (95% CI, 9.9 to 11.2) lower for RN compared with PN around the 1-year mark (Figure 2, Supplemental Figure 1). One randomized trial noted a mean difference in absolute eGFR of 14.1 ml/min per 1.73 m² in favor of PN at 1 year (6). Significant heterogeneity for mean change in eGFR was observed.

Subgroup analyses showed similar overall findings in studies including T1a, T1b, and T2 tumors, with two studies
<table>
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NA, not applicable.
Figure 2.  Mean change in eGFR shown to favor partial nephrectomy (PN) and thermal ablation (TA) over radical nephrectomy (RN) on meta-analysis. The comparisons shown are (A) RN versus PN, (B) RN versus TA, and (C) PN versus TA. The widths of the horizontal lines represent the 95% confidence intervals (95% CIs) for each study. The diamonds at the bottoms of the graphs indicate the 95% CIs. WMD, weighted mean difference.
reporting nonsignificant trends toward poorer renal outcomes for RN in tumors 4–7 or >7 cm (24,29). Elderly and young patients both experienced similar 8- to 15-ml/min per 1.73 m² lower eGFR decreases with RN compared with PN. The interaction of prior CKD with eGFR change was less clear. One study showed the observed benefit in eGFR for PN over RN similar for patients with preoperative eGFR >60 or <60 ml/min per 1.73 m², but two studies suggested that there was an attenuated difference for patients with preexisting CKD stage 3 (15,22,35). The absolute final eGFR values in all cases were, as expected, worse for patients with preoperative CKD. Another study suggested greater decreases in absolute eGFR for patients with higher preoperative eGFR (21). Taken together, the immediate clinical effect of management strategy to patients with preexisting CKD is likely greater, with categorical CKD outcomes potentially being more important than absolute changes. There is also the suggestion of greater preservation of eGFR with PN compared with RN than previously recognized for patients with eGFR >60 ml/min per 1.73 m², although the long-term effect is not yet known.

Eleven studies reported long-term trends in creatinine and/or eGFR, showing an initial drop in the immediate postoperative period followed by improvement until approximately 3–6 months (6,12,14,17,19,25,28,32,37,39,42). At this point, levels stabilized for as long as 10–15 years (6). Three studies suggested that the lower final eGFR for RN occurred, because an equivalent improvement in eGFR in the 3- to 6-month time window was not present (17,25,32).

Categorical Outcomes. A total of 24 studies assessed categorical renal functional outcomes for RN versus PN, including one randomized trial and two population-based studies (Table 2) (6,14,15,18,19,21–25,27,28,31,34–38,40,41,44–47). The majority addressed incidence of CKD stage 3 (21 studies), and ten studies reported incidence of ESRD. Meta-analyses showed higher risk of CKD stage 3 (Figure 3) for RN compared with PN (relative risk [RR], 2.56; 95% CI, 1.97 to 3.32). Parallel findings were noted for ESRD (Supplemental Figure 2). Similar results were observed on meta-analyses using cutoffs for CKD stages ≥3 and ≥4, but the latter had only included studies and was not statistically significant. One randomized trial reported >20% higher rate of CKD stage 3 for patients undergoing RN compared with PN on the basis of both the lowest eGFR or the last eGFR during follow-up (6). Similar findings were also observed across tumor sizes and age groups, although the absolute risk in elderly patients was two to four times higher than in younger patients, despite similar baseline eGFR (23).

Again, the effect of prior CKD on categorical outcomes was uncertain given the sparsity of studies and sample sizes. One study suggested that patients with CKD stage 3 had a statistically significant worsening of CKD stage after RN compared with PN, but another study found the association to be nonsignificant on multivariable analysis (odd ratio, 1.59; 95% CI, 0.83 to 3.04) (35,44). Samples sizes for patients with CKD stage 3b or 4 undergoing surgery were even smaller and did not provide sufficient evidence for interpretation.

RN versus TA

Continuous Outcomes. A total of seven studies assessed continuous renal functional outcomes, showing generally worse outcomes for RN compared with TA (15,30–35). The median decrease was 10.3 ml/min per 1.73 m² lower with RN than with TA, and meta-analysis showed similar difference in mean eGFR of 9.94 ml/min per 1.73 m² (95% CI, 7.61 to 12.26) (Figure 2, Table 1). The majority of studies (five of seven) reported statistically significant associations.

Categorical Outcomes. Four studies compared categorical outcomes for RN versus TA, showing greater incidence of CKD stage 3 for RN (RR, 3.48; 95% CI, 1.08 to 11.15) on meta-analysis (15,31,34,45) (Figure 3). The incidence rates of higher stages of kidney dysfunction were not consistently compared (Table 2).

PN versus TA

Continuous Outcomes. A total of 20 studies assessed continuous renal functional outcomes, showing similar changes for PN compared with TA (15,30–34,49–62) (Table 1). Meta-analyses showed a larger mean increase in creatinine of 0.07 mg/dl (95% CI, 0.00 to 0.15) and a larger mean decrease in eGFR of 1.0 ml/min per 1.73 m² (95% CI, −0.2 to 2.1) for PN compared with TA, but neither was statistically significant (Figure 2, Supplemental Figure 1). Studies specifically evaluating T1a tumors had similar findings, and demographic factors were not associated with change in eGFR. Two studies showed similar outcomes among patients with solitary kidneys, whereas another study found larger decrease in eGFR for patients with preoperative CKD stage 3 who received TA (51,58,60). Interestingly, one study reported that higher baseline eGFR was associated with greater postoperative decrease in a series of solitary kidneys (58). For long-term trends, most studies reported that the decrease in eGFR for PN and TA postoperatively remained relatively stable, whereas two noted that PN may have had a greater decrease 1 day after surgery but then recovered to similar levels as TA by 1–6 months (30,32,49,53,61,62).

Categorical Outcomes. A total of 11 studies assessed categorical outcomes and showed similar incidence of kidney dysfunction for PN versus TA (Table 2) (15,31,34,45,49,51,53,55,57,58,60). Meta-analyses showed similar rates of CKD stage 3 (RR, 1.14; 95% CI, 0.77 to 1.67) and ESRD (RR, 0.92; 95% CI, 0.19 to 4.39) (Figure 3, Supplemental Figure 2).

AS versus Other Management Strategies

Continuous Outcomes. Only two studies compared continuous renal functional outcomes of AS with other management strategies (34,63). One included patients ages 75 years old and older and showed a statistically significant decrease of 10 ml/min per 1.73 m² for RN compared with 3 ml/min per 1.73 m² for AS (63). The second study compared all four management strategies and showed greater decrease in mean eGFR for RN compared with AS, PN, and TA (34). No uncontrolled AS study reported renal functional outcomes.

Categorical Outcomes. The same two studies assessed categorical outcomes, which were generally more favorable for AS than RN. One study showed the incidence of new CKD stage 3 to be about 5.8% for AS versus 76% for RN,
Table 2. Categorical renal functional outcomes for radical nephrectomy versus partial nephrectomy, radical nephrectomy versus thermal ablation, and partial nephrectomy versus thermal ablation

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NA, not applicable.
Figure 3. Incidence of stage 3 CKD shown to favor partial nephrectomy (PN) and thermal ablation (TA) over radical nephrectomy (RN) on meta-analysis. The comparisons shown are (A) RN versus PN, (B) RN versus TA, and (C) PN versus TA. The widths of the horizontal lines represent the 95% confidence intervals (95% CIs) for each study. The diamonds at the bottoms of the graphs indicate the 95% CIs. RR, risk ratio.
whereas the other study reported 3% for AS, 2% for PN, 0% for TA, and 40% for RN at the end of follow-up (34,63).

**AKI**

Meta-analyses showed no overall difference in the rate of AKI for RN versus PN with RR, 1.3 (95% CI, 0.9 to 2.0) (12,14,16,19,26,33,34,45,46,64–67) (Figure 4). However, a subset of four studies evaluating T1a tumors found that rates of AKI were higher for RN compared with PN (RR, 1.37; 95% CI, 0.9 to 2.8) (33,45,48) (Figure 4). Similarly, three studies compared RN with TA, showing that RN was generally associated with a higher rate of AKI, but results on meta-analysis were not statistically significant (RR, 1.6; 95% CI, 0.9 to 2.8) (33,45,48) (Figure 4). Rates of AKI for PN versus TA were comparable among six studies with RR, 1.0 (95% CI, 0.6 to 1.9) (Figure 4) (33,45,49,50,57,58).

**Strength of Evidence and Risk of Bias**

Strength of evidence is given with each comparison, and it was, at best, moderate or low for many outcomes and often insufficient for comparisons involving AS (Supplemental Table 1). Overall risk of bias was moderate for 30 of the 52 cohort studies (Supplemental Figure 3). Funnel plots suggested potential publication bias for the outcome of CKD stage 3 for RN versus PN but none of the other comparisons (Supplemental Figure 4).

**Discussion**

The evidence regarding management strategies of renal masses suspicious for localized renal cell carcinoma is almost entirely on the basis of retrospective studies and susceptible to the inherent limitations of the study design. However, a number of comparative studies included renal functional

![Figure 4](image-url)
outcomes evaluating RN, PN, TA, and AS along with a randomized trial comparing RN with PN. Strength of evidence was low to moderate for most comparisons and outcomes, with notable findings of generally worse decrease in eGFR and incidence of CKD for RN compared with other management strategies and similar postoperative renal function for PN compared with TA. A few small studies compared management strategies among patients with preexisting CKD, with some suggestion that RN led to a greater incidence of progressive CKD compared with PN. AS was associated with better renal functional outcomes compared with RN, but evidence was insufficient for comparisons with PN or TA.

Current guidelines do not strictly define preference for management strategy on the basis of renal functional outcomes, and the last update to the AUA guidelines focused largely on absolute creatinine values (3,7). However, all available management strategies have shown generally favorable survival outcomes, leading to a greater focus on morbidity due to postoperative changes in renal function (4). The one randomized trial comparing RN with PN noted greater preservation of renal function with PN but counterintuitively, suggested worse overall survival for PN, despite similar cancer-specific survival (6). Critics note that the trial was underpowered for survival outcomes and experienced significant crossover. In patients with a solitary kidney, nephron-sparing approaches are preferred when possible, because RN leads to ESRD and an immediate need for hemodialysis.

By extrapolation, a dose-response rationale would argue in favor of nephron-sparing surgery for patients with preexisting CKD, where RN may be expected to have a worse effect on postoperative renal function. Surprisingly, very few studies compared RN with other modalities among patients with CKD, with some showing worse outcomes for RN compared with PN, whereas others could not show a
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statistically significant difference (15,22,35,44). The most clearly shown benefit was for patients with preserved kidney function (stages 1 and 2), but there were limited data on higher levels of kidney dysfunction (35). Larger studies with longer follow-up are needed to better quantify the magnitude of benefit for PN compared with RN in these patients.

In recent years, the concept of surgically induced CKD has been introduced, where a given stage of surgical CKD may have a different long-term prognosis compared with a similar degree of medical CKD. The thought is that the destruction or removal of nephrons results in a measurable decline in eGFR, whereas any progressive decline in medical CKD is a function of preexisting comorbidities. Indeed, one study showed that progressive decline in renal function was worse for an independent cohort of patients with CKD who did not have surgery compared with patients who had CKD after surgery for a renal mass (68). For patients undergoing surgery, we found an initial drop in creatinine and eGFR in the immediate postoperative period, with some recovery up to 3–6 months followed by stabilization for up to 10–15 years (6,12,14,17,19,25,28,32,37,39,42).

Therefore, the relative long-term renal functional benefit of nephron-sparing options over RN may depend on the degree of preexisting medical comorbidities that could act as lifelong insults on renal function. For patients with CKD and poorly controlled comorbidities, the benefit of PN over RN will likely be augmented. In fact, noncancer-related mortality may be lower for surgical CKD than medical CKD (68). Evidence has suggested that renal function and cardiovascular health are intimately related, and it is known that the presence of CKD is associated with worse outcomes among patients with cardiovascular disease (69). However, the rate of cardiac events and cardiovascular-specific survival has been actively studied among patients undergoing PN and RN without definitive results (70–72).

Among nephron-sparing interventions, the comparison of PN and TA has driven notable attention of the primary options for management. TA is considered a less invasive option and generally reserved for older patients or patients with comorbidities, making surgery a less attractive option (3). TA is associated with a greater rate of persistent or recurrent local disease after a single treatment session, but the current evidence does not support significant differences in survival compared with PN (4). Notably, our meta-analyses showed similar change in eGFR, incidence of CKD, and rates of AKI for PN versus TA. Therefore, the decision to pursue PN or TA should largely be on the basis of a balance between oncologic outcomes and complication rates.

Limitations of the systematic review deserve mention. Risk of bias assessment showed moderate selection bias for most of the comparative cohort studies. Additionally, some studies were excluded due to imprecise or lack of reporting of clinical stage, making comparisons between management strategies difficult to interpret. Other potentially relevant outcomes, including proteinuria and cardiovascular disease, were generally not reported. Lastly, studies were inconsistent in the timeframe for which renal functional outcomes were reported. It has been recommended that, at a minimum, preoperative, 1 month, and 12 months values for eGFR be reported to allow comparable timeframes between studies (73).

Renal functional implications vary for different approaches to management of renal masses suspicious for localized renal cell carcinoma. Comparative studies indicate worse postoperative renal function for patients undergoing RN compared with other strategies. Renal functional outcomes are generally comparable for PN and TA, shifting the focus to a balance of oncologic outcomes and complications. Research on AS is limited and deserves further attention to identify appropriate patients who can safely maximize renal preservation without sacrificing oncologic outcomes. Long-term follow-up is needed for patients with preexisting CKD to quantify the full benefits of nephron-sparing approaches in avoiding progressive CKD and ESRD compared with RN.

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Disclosures
None.

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