Comparative Effectiveness for Survival and Renal Function of Partial and Radical Nephrectomy for Localized Renal Tumors: A Systematic Review and Meta-Analysis

Simon P. Kim, R. Houston Thompson, Stephen A. Boorjian, Christopher J. Weight, Leona C. Han, M. Hassan Murad, Nathan D. Shippee, Patricia J. Erwin, Brian A. Costello, George K. Chow and Bradley C. Leibovich*

From the Departments of Urology (SPK, RHT, SAB, CJW, JJK, GKC, BCL) and Oncology (BAC), Knowledge and Evaluation Unit (LCH, MHM, PJE) and Division of Health Care Policy and Research (NDS), Mayo Clinic, Rochester, Minnesota

Purpose: The relative effectiveness of partial vs radical nephrectomy remains unclear in light of the recent phase 3 European Organization for the Research and Treatment of Cancer trial. We performed a systematic review and meta-analysis of partial vs radical nephrectomy for localized renal tumors, considering all cause and cancer specific mortality, and severe chronic kidney disease.

Materials and Methods: Cochrane Central Register of Controlled Trials, MEDLINE®, EMBASE®, Scopus and Web of Science® were searched for sporadic renal tumors that were surgically treated with partial or radical nephrectomy. Generic inverse variance with fixed effects models were used to determine the pooled HR for each outcome.

Results: Data from 21, 21 and 9 studies were pooled for all cause and cancer specific mortality, and severe chronic kidney disease, respectively. Overall 31,729 (77%) and 9,281 patients (23%) underwent radical and partial nephrectomy, respectively. According to pooled estimates partial nephrectomy correlated with a 19% risk reduction in all cause mortality (HR 0.81, $p < 0.0001$), a 29% risk reduction in cancer specific mortality (HR 0.71, $p = 0.0002$) and a 61% risk reduction in severe chronic kidney disease (HR 0.39, $p < 0.0001$). However, the pooled estimate of cancer specific mortality for partial nephrectomy was limited by the lack of robustness in consistent findings on sensitivity and subgroup analyses.

Conclusions: Our findings suggest that partial nephrectomy confers a survival advantage and a lower risk of severe chronic kidney disease after surgery for localized renal tumors. However, the results should be evaluated in the context of the low quality of the existing evidence and the significant heterogeneity across studies. Future research should use higher quality evidence to clearly demonstrate that partial nephrectomy confers superior survival and renal function.

Key Words: kidney; carcinoma, renal cell; renal insufficiency; nephrectomy; mortality

Abbreviations and Acronyms

ACM = all cause mortality
AUA = American Urological Association
CKD = chronic kidney disease
CSM = cancer specific mortality
EORTC = European Organisation for Research and Treatment of Cancer
PN = partial nephrectomy
RCC = renal cell carcinoma
RCT = randomized, controlled trial
RN = radical nephrectomy
SRM = small renal mass

Submitted for publication November 15, 2011.

Study received institutional review board approval.

Supported by Healthcare Delivery Research Scholars Program, Mayo Clinic.

Supplementary material, including references 31 to 46, for this article can be obtained at http://jurology.com.

* Correspondence: Department of Urology, Mayo Clinic, 200 First St. Southwest, Rochester, Minnesota 55905 (e-mail: Leibovich.Bradley@mayo.edu).

In 2010 RCC remained the third most commonly diagnosed genitourinary malignancy with an estimated 58,240 incident cases and 8,210 cancer related deaths in the United States.[1] Along with the increase in SRMs,[2,3] concomitant trends toward renal tumor downward stage migration and smaller size at RCC diagnosis have significantly altered the clinical presentation, such

0022-5347/12/1881-0051/0
THE JOURNAL OF UROLOGY®

Vol. 188, 51-57, July 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2012.03.006

that T1 tumors now account for more than a majority of incident cases.[4]

Clinical guidelines were recently changed to recommend performing PN for T1 renal tumors when technically feasible, based on primary renal tumor size and site.[5–7] The recommendations are in response to observational studies suggesting equivalent oncological outcomes and superior overall survival due to the lower risk of adverse renal outcomes for PN than for RN.[8–12] However, the EORTC RCT of PN and RN recently showed conflicting results that survival and renal function are similar for the 2 procedures.[13] This multi-institutional phase 3 RCT suggests that aggressive PN may be inappropriate, given the increasing adoption of PN and limited level 1 evidence documenting any relative efficacy.[13–15] Moreover, sparse data are available on patients and providers for pooled estimates of the treatment effect of PN vs RN on survival and the risk of severe CKD.

In this context we performed a systematic review and meta-analysis of the comparative effectiveness of PN and RN for ACM, CSM and CKD. We ascertained pooled estimates of each outcome for localized renal tumors.

METHODS

Data Source and Search Strategy

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Scopus and Web of Science from inception to February 2011 using a search strategy similar to that of the AUA clinical guidelines. The search terms used to identify potentially eligible studies from each data source were renal mass, renal cell carcinoma, renal neoplasm, nephron-sparing surgery, partial or radical nephrectomy, nephrectomy or renal surgery. This search strategy allowed us to include benign and malignant renal tumors.

Study Outcomes

The primary study outcomes were ACM and CSM. The secondary outcome was severe CKD after surgery. Each study in our systematic review assigned a CKD stage using the estimated glomerular filtration rate or receipt of hemodialysis.[16] Due to the heterogeneity of defining CKD severity across studies we pooled the studies for stages III-V or IV-V, as determined by the estimated glomerular filtration rate or by hemodialysis, to define progression to severe CKD postoperatively.

Analysis

Subgroup. To explore possible causes of heterogeneity across studies we determined a priori to perform several subgroup analyses by publication year, patient sample type and benign vs malignant renal tumor pathology.

Statistical. Primary and secondary outcomes were synthesized from the estimates of each study to enumerate pooled HRs and 95% CIs. Meta-analyses were done using generic inverse variance, fixed effects models to determine the HR of ACM, CSM and severe CKD after surgery. Data from studies that included benign renal tumors did not contribute to the CSM pooled estimate. The I^2 statistic was used to quantify the proportion of heterogeneity across studies due to real differences in clinical or methodological characteristics rather than to chance alone.[17] To assess finding robustness we also used a random effects model to ascertain the effects of variance and heterogeneity on sensitivity analysis. Statistical analysis was done using RevMan 5.1 and Stata®/MP, version 11.0.

RESULTS

Data Retrieval

Our search strategy yielded 665 studies that met the inclusion criteria. Upon the completion of primary and secondary screenings 39 studies were identified as eligible for this systematic review (fig. 1). However, we excluded 3 nonEnglish language studies due to insufficient data. Thus, 36 studies were selected for meta-analysis, including a total of 41,010 patients who underwent nephrectomy for localized renal tumors, of whom 31,729 (77%) and 9,281 (23%) were treated with RN and PN, respectively.

Study Characteristics

Although several population based studies used historical cohorts or a case control design, most originated from retrospective institutional data. Of the 36 series selected for meta-analysis 21 described the primary outcome of ACM,[10–13,18] 21 described CSM[13,18–25] and 9 described CKD severity after nephrectomy.[9,10,22,26] In only 5 studies were population based data used to examine the comparative outcomes of PN and RN.[8,10,20,27]

Outcomes

Overall the pooled HR correlated with a 19% risk reduction in ACM in favor of PN (HR 0.81, $p < 0.00001$, fig. 2). Compared to RN, PN also correlated with a 29% decreased likelihood of CSM (HR 0.71, $p = 0.0002$, fig. 3). The meta-analysis of the secondary outcome regarding functional renal outcome indicated that PN was associated with a decreased risk of severe CKD in favor of PN (fig. 4).

In a study using SEER (Surveillance, Epidemiology and End Results)-Medicare data Miller et al stratified the risk of severe CKD by time.[10] To minimize bias we included each estimate of the risk of end stage renal disease for each interval. The strongest treatment effect was noted for a 61% risk reduction in severe CKD associated with PN (HR 0.41, $p < 0.00001$). However, on each meta-analysis we observed moderate to high heterogeneity across studies (I^2 statistic 49% to 87%).

Study Quality

Most groups relied on retrospective institutional data from historical cohort or on case-control study designs. Only 1 series provided prospective data or

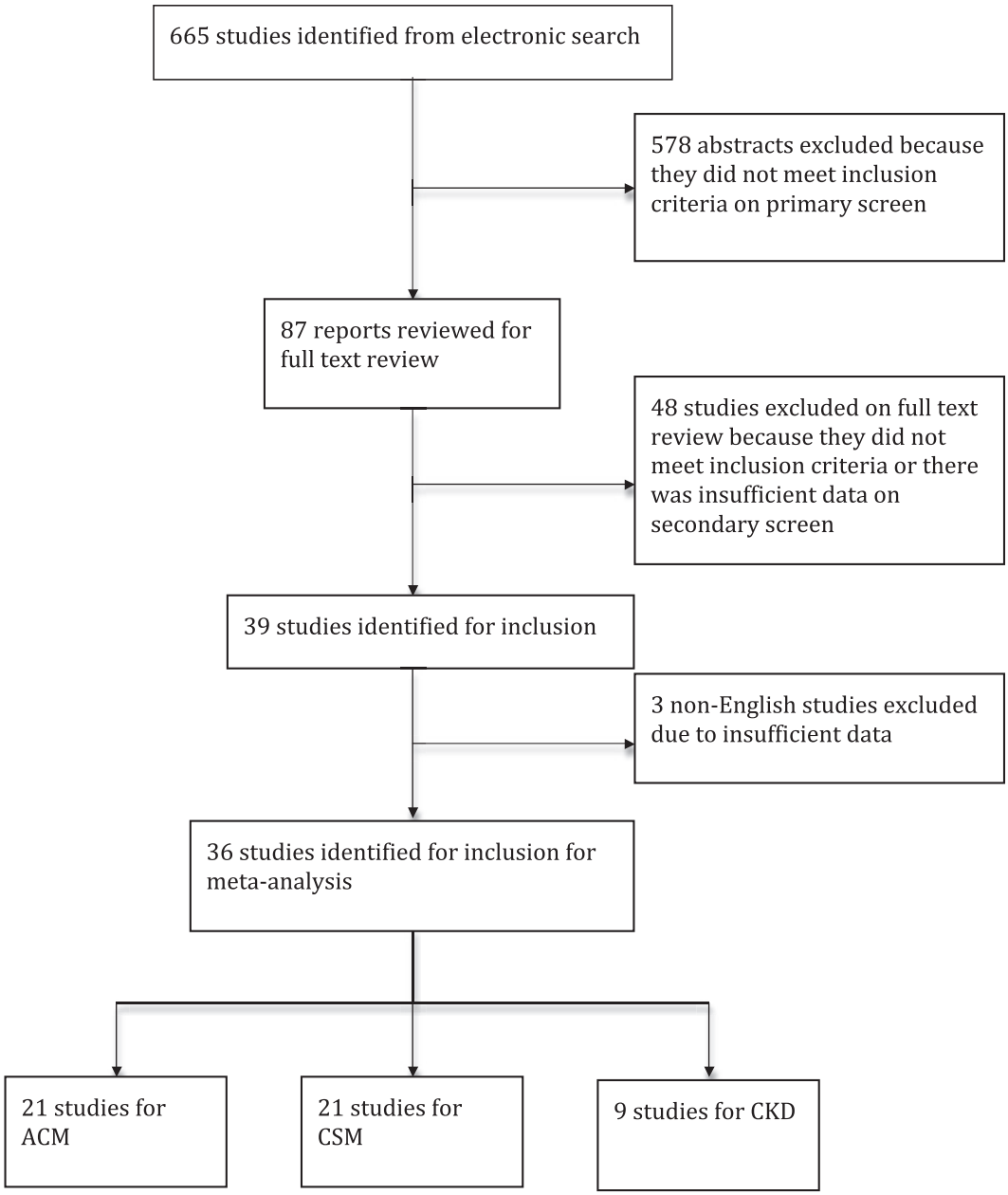

Figure 1. Study attrition

the highest level of evidence from an RCT.[13] Seven of the 36 studies (19%) provided information on patients lost to followup. While the EORTC RCT had adequate allocation concealment through central randomization, its major limitations were the loss to followup of about 10% of patients and significant crossover with switched treatment in 55, that is 16 (5.9%) randomized to RN underwent PN and 39 (14.6%) randomized to PN underwent RN.

Subgroup and Sensitivity Analyses

Table 1 shows subgroup analysis by publication year, population based vs single institution patient sample and benign vs malignant renal mass. When stratified by publication year, there were significant differences in pooled ACM HRs from publication years 1995 to 2005 vs 2006 to 2010 ($p = 0.03$) and between studies using institutional vs population based cohorts ($p = 0.04$). However, we observed minimal differences in ACM whether studies used benign or malignant renal masses.

CSM subgroup analysis revealed that a single population based study was responsible for weighting the pooled estimate for the lower risk of CSM associated with PN.[20] Due to the observed heterogeneity in outcome according to patient population source, excluding this single SEER-Medicare study

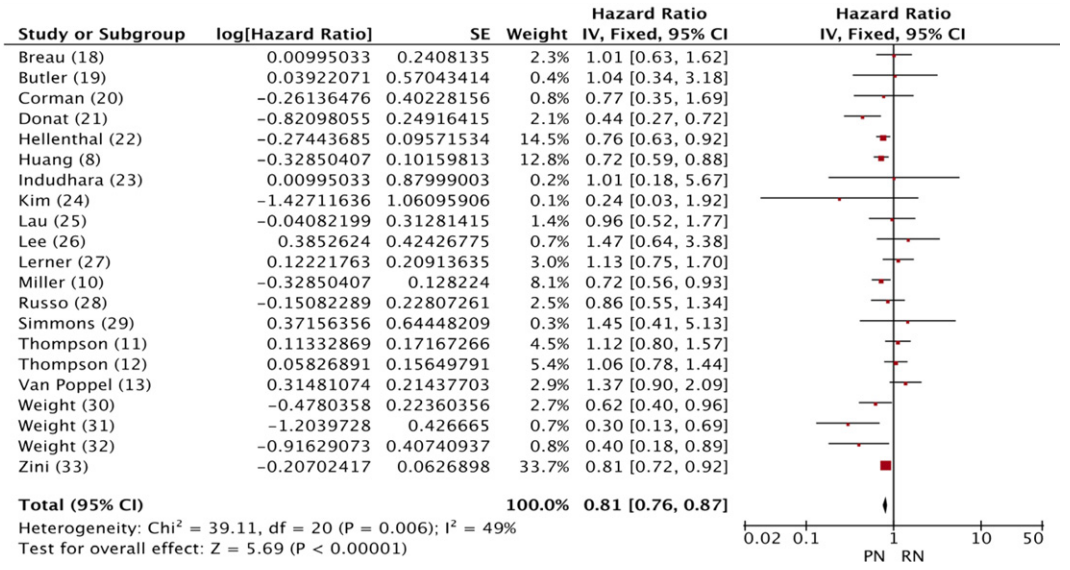

Figure 2. Forest plot of pooled ACM HRs for PN vs RN in 21 studies

yielded CSMs for PN and RN similar to those of institutional series (HR 0.98, 95% CI 0.79–1.22). Likewise the SEER-Medicare population study also explained the differences by publication year (p = 0.004). Conversely, institutional series revealed a stronger treatment effect for a lower incidence of severe CKD for PN despite significant differences in population based and historical cohort studies (p <0.001). Using random effect models pooled estimates of surgery type remained robust only for ACM (HR 0.81, p = 006) and severe CKD after surgery (HR 0.40, p <0.0001, table 2). However, the generic inverse variance with random effects indicated that PN was no longer significant for CSM (HR 0.79, p = 0.17). Random effect values less than 1.00 favored PN for each outcome.

DISCUSSION

In our systematic review we synthesized the existing evidence to compare 2 types of commonly performed renal operations for localized renal tumors to ascertain pooled estimates of the treatment effect on

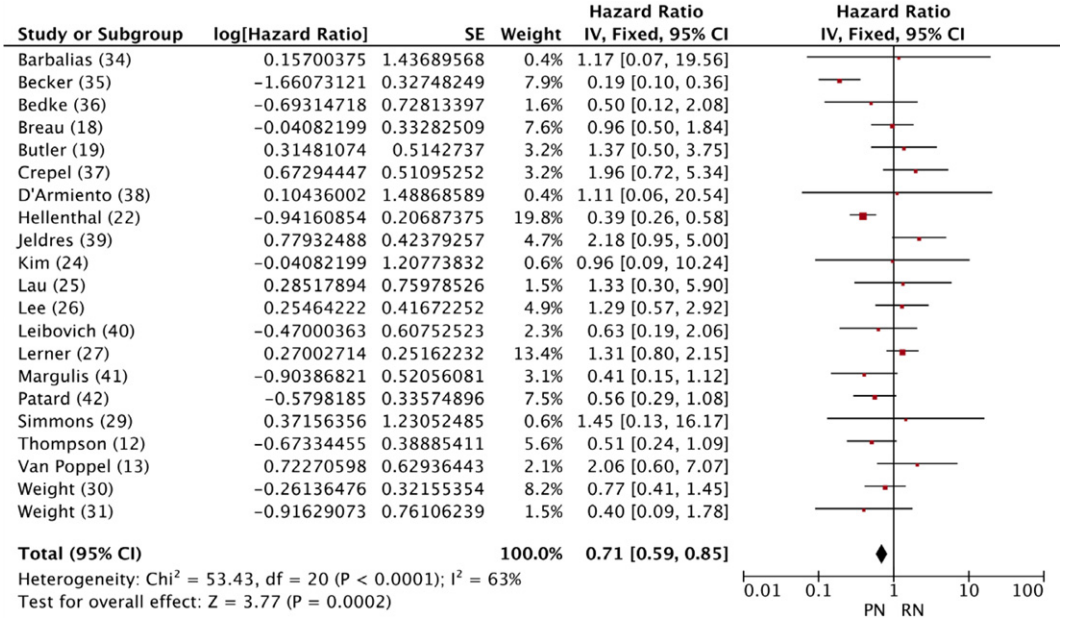

Figure 3. Forest plot of pooled CSM HRs for PN vs RN in 21 studies

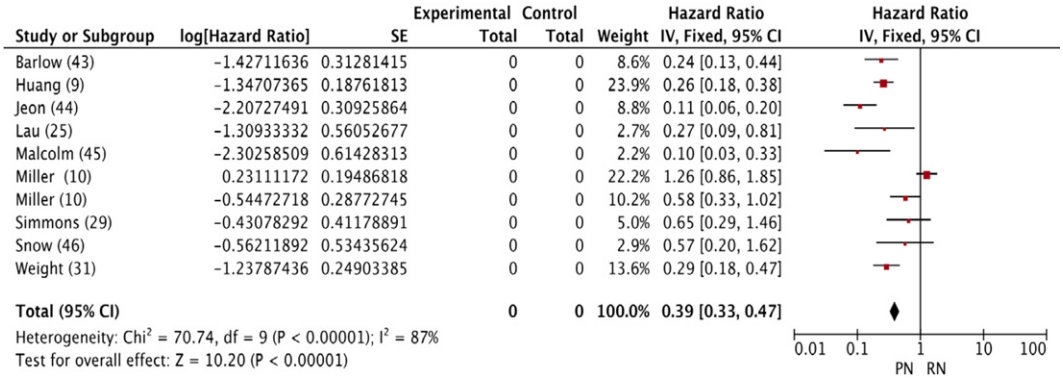

Figure 4. Forest plot of pooled severe CKD HRs for PN vs RN in 9 studies

survival and renal function, evaluate evidence quality and reconcile the conflicting results of the EORTC RCT with those of observational studies. Historically RN has been considered the gold standard for localized renal tumors. PN was initially indicated for localized renal tumors in a solitary kidney to avoid the morbidity associated with severe CKD and dialysis. Since growing evidence suggests that the decreased morbidity of severe CKD associated with PN may benefit patients by also decreasing the risk of ACM, clinical guidelines recommend PN as the preferred treatment for T1 renal tumors.[5–7] National trends of increased PN use for RCC indicate that urologists have been responsive to the growing evidence and clinical guidelines.[14,15] However, the EORTC RCT of clinical T1–T2 renal tumors treated with PN or RN conflicts with existing guidelines and previous observational studies.[13]

Table 1. *Subgroup analysis of ACM, CSM and severe CKD by publication year, patient sample and renal mass type*

	HR (95% CI)	p Value
	ACM	
Publication yr:		
1995–2005	1.08 (0.80–1.41)	0.03
2006–2011	0.80 (0.74–0.86)	
Pt sample:		
Single institution	0.91 (0.80–1.04)	0.04
Population based	0.77 (0.71–0.84)	
Renal mass:		
Benign	0.56 (0.32–0.98)	0.18
Malignant	0.82 (0.76–0.88)	
	CSM	
Publication yr:		
1995–2005	1.03 (0.75–1.40)	0.004
2006–2011	0.59 (0.47–0.73)	
Pt sample:		
Single institution	0.98 (0.79–1.22)	0.001
Population based	0.49 (0.34–0.71)	
	Severe CKD	
Pt sample:		
Single institution	0.25 (0.20–0.31)	<0.001
Population based	0.99 (0.72–1.35)	

Our study provides several important findings that help reconcile differences between RCTs and observational studies while also highlighting evidence quality. Overall results reveal that PN is associated with a lower risk of ACM, CSM and severe CKD compared to RN. Analysis suggests that PN confers a 19%, 29% and 61% risk reduction for ACM, CSM and severe CKD, respectively. These findings should be viewed against the significant heterogeneity across studies, limited data from multiple RCTs and the use of mostly historical cohort studies, which are prone to selection bias. Furthermore, the pooled estimates of the PN treatment effect are limited by the lack of robustness in consistent findings from sensitivity and subgroup analyses. The lower CSM for PN represented an unanticipated finding in our study, given the paucity of evidence of such a benefit and the fact that clinical guidelines base recommendations on an equivalent oncological outcome. A single, population based study using SEER-Medicare data with analysis limited to octogenarians who underwent PN or RN for RCC is responsible for this CSM finding.[20] Its exclusion from subgroup analysis indicated that PN and RN conferred equivalent CSMs.

Although our findings suggest that PN lowers the risk of ACM and postoperative severe CKD, it is also essential to critically examine the quality of evidence from included studies that served in large part as the basis for best practice guidelines for surgical management of localized renal tumors. The validity of our results and inferences about the pos-

Table 2. *Meta-analysis of PN vs RN for ACM, CSM and CKD from generic inverse variance model with random effects*

	HR (95% CI)	p Value
ACM	0.81 (0.76–0.87)	0.006
CSM	0.79 (0.57–1.11)	0.17
Severe CKD	0.34 (0.20–0.58)	<0.0001

sible benefits of PN are only as strong as the quality of the existing evidence.

We evaluated the quality of evidence of the single RCT, ie the strength of inference, using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework, which has been used in medical and surgical settings.[13] While Van Poppel et al should be credited with performing a surgical phase 3 RCT of PN and RN, the evidence derived from this clinical trial, which would usually be high, was downgraded due to imprecision with a small sample size and wide CIs as well as methodological limitations, including substantial loss to followup and crossover rates. This study was also closed due to poor accrual and, thus, it was underpowered to detect a difference in outcome.

Since our systematic review relied mostly on observational studies, the evidence is also low, considering the observational nature of these studies, the risk of selection bias and the statistical heterogeneity noted in our analysis. Thus, the strength of inference from each body of evidence is associated with some degree of uncertainty.

For the AUA guidelines on SRM a systematic review was done of PN, RN, ablation and active surveillance, including a literature search up to 2007. Guidelines from the AUA, European Association of Urology and National Comprehensive Cancer Network recommend PN for SRMs amenable to surgical resection.[5–7] Our results, which are consistent with these recommendations to some extent, bring the evidence up to date. Nevertheless, our systematic review indicates the level of uncertainty caused by low quality evidence. Thus, treatment decisions should rely on our findings while acknowledging the uncertainty of evidence, and incorporating patient preference, surgeon expertise and the clinical context, such as comorbidity, life expectancy and patient functional rather than chronological age.

Our inferences about optimal treatment for localized renal tumors, whether with PN or RN, have several limitations. Although systematic reviews and meta-analyses are considered high level evidence in many regards, our results relied mostly on observational studies with only 1 RCT. As a result, it is difficult to conclusively state that PN provides superior survival and renal function outcomes after surgery. The treatment decision to perform PN or RN remains highly complex and must balance the benefit and harm of different alternatives, and incorporate other clinical considerations. We did not review and synthesize the evidence to assess the relative differences in the harm of PN and RN, such as postoperative complications. However, previous studies have to date shown little difference in postoperative complications by surgery type except for a modestly higher risk of postoperative bleeding for PN. Another important limitation is that few studies incorporated comorbidity or provide competing risk analyses to elucidate the relative effectiveness of PN and RN. Our systematic review did not evaluate other possible treatment alternatives, such as ablation or surveillance. We limited the evidence synthesis to PN vs RN since we thought that this question was the most clinically relevant one in light of the recent EORTC trial. Our meta-analysis likely included some patient overlap, particularly for studies using population based SEER data. We may have overestimated the treatment effect from the pooled estimates of PN and RN, although we did in part address this limitation in our subgroup analysis.

While our study shows the potential benefits of PN over RN for SRMs, the low quality of available evidence leaves patients, urological surgeons and policymakers with some remaining uncertainty. In light of our findings it is essential to note that the absence of high quality evidence should not be translated into an absence of treatment benefit from PN until we have clear evidence indicating minimal differences in outcomes between PN and RN. Nonetheless, future research should address the critical limitations of the existing evidence to clearly answer whether PN provides superior patient centered outcomes compared to RN. Although performing a well designed RCT of PN and RN for SRMs would be ideal, it is arguable whether such a RCT could be successfully done in the United States. Until we have such high level evidence our study suggests that PN should remain the preferred treatment for localized renal tumors.

CONCLUSIONS

While the available evidence is of low quality, our study suggests that PN is associated with a lower risk of ACM, CSM and severe CKD. Patients diagnosed with localized renal tumors should be appropriately counseled that PN confers advantages in renal function and survival but they should also be made aware of the uncertainty of the evidence.[28–30]

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