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Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

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Abstract

Background: Stage T1a renal cell carcinoma (RCC, < 4 cm) is usually incidentally detected and curable. Nephron-sparing, partial nephrectomy (PN) has replaced radical nephrectomy (RN) as standard of care. RN remains the 2nd line treatment option, while percutaneous ablation (PA), a newer, nonsurgical treatment, remains a 3rd line option due to a relative paucity of data.

Objective: To compare PA, PN and RN outcomes.

Design: Propensity score-based inverse probability of treatment weighted comparison of prospectively gathered population-level registry data.

Setting: SEER-Medicare linked files 2006–2013.

Patients: Ages 66 and older treated for T1a renal cancers from 2006–2011.

Interventions: PA vs. PN and RN.

Measurements: RCC-specific and overall survival, 30- and 365-day post-intervention cumulative complications.

Results: 4310 patients had median follow-up of 52 months for overall survival and 42 months for RCC-specific survival. 5-year RCC-specific survival after PA vs. PN and vs. RN was 95 (95% CI 93–98) vs. 98% (96–99) and 96 (94–98) vs. 95% (93–96). 5-year post-PA overall survival vs. PN was 77 (74–71) vs. 86% (84–88) and vs. RN was 74 (71–78) vs. 75% (73–77). Cumulative rates of renal insufficiency 31–365 days after PA, PN, and RN were 11% (8–14), 9% (8–10) and 18% (17–20). Rates of non-urologic complications within 30 days after PA, PN and RN were 6% (4–9), 29% (27–30) and 30% (28–32). Ten percent of PN patients were converted intraoperatively to RN. Seven percent of PA patients received additional PA within 1 year of treatment.

Limitations: These observational data may be affected by residual confounding from selection bias toward younger, healthier patients in the PN group. Findings from this older study population

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are likely less applicable to younger patients. Use of SEER-Medicare linked files prevented analysis of patients treated after 2011, which may reduce generalizability to the newest PA, PN and RN techniques.

Conclusions: For well-selected older stage T1a renal cancer patients, PA may offer similar oncologic outcomes, less long-term renal insufficiency and markedly fewer perioperative complications compared to RN. PA may also offer oncologic outcomes approaching those of PN, with fewer perioperative complications.

Registration: None.

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INTRODUCTION

Most older patients diagnosed with renal cell carcinoma (RCC) will not die from this usually indolent cancer [1,2]. Now routinely found incidentally during imaging for other indications, most RCCs are still localized within the renal capsule (Stage T1) and curable [3]. Small renal masses, those under 4 cm diameter corresponding to RCC stage T1a, now comprise 48–66% of all renal tumors [4]. Partial nephrectomy (PN), a nephron-sparing treatment, has become the standard of care for T1a RCC [5–8]. However, rates of PN have plateaued at around 40% of all localized RCC treatments [2,9].

Thermal ablation is another nephron-sparing treatment that destroys cancer using heat or cold emanating from needles placed within renal tumors. Ablation is increasingly being performed percutaneously (PA) in an interventional radiology suite under image guidance rather than laparoscopically in an operating room [10]. Because only about 20% of localized RCCs are aggressive, another alternative for older or chronically ill patients is primary imaging surveillance, with intervention only if rapid tumor growth signals a higher risk of metastasis [5–8,11]. A potential liability of surveillance is that patients may be referred for treatment after tumor growth, and larger tumor diameter is a leading risk factor for ablation-related complication and treatment failure [12].

In keeping with professional society guidelines, most stage T1a patients not treated with PN will receive radical nephrectomy (RN) [5–8,13]. However, renal insufficiency is a relatively common complication of RN that carries its own significant risk of death; and while renal function decreases with age, older T1a RCC patients are more likely than their younger peers to be treated with RN instead of PN [13–17]. In contrast, most urology and cancer society guidelines recommend that ablation only be considered for patients who are poor surgical candidates, therefore PA is utilized for only about 10% of localized renal masses [5–8,10]. Specific reasons cited for limited utilization include a lack of 5-year comparative PA outcomes data, lack of biopsy proof of malignancy in PA studies, and a higher post-PA local recurrence rate compared to PN or RN [5–8].

A recent meta-analysis commissioned by the Agency for Healthcare Research and Quality (AHRQ) criticized the entirety of localized RCC management literature as being at moderate to serious risk of treatment selection bias due to a lack of prospectively acquired, comparative data [18]. There has been only one randomized controlled trial (RCT) comparing PN to RN and one smaller trial comparing laparoscopic and open surgical ablation to PN [19,20]. The PA literature, in particular, lacks prospective, comparative data. A meta-analysis of single-center, single cohort, mostly retrospective studies found ablation to be safer than PN, with similar 5-year RCC-specific survival [21]. Though, to date, no RCT has compared PA to PN or RN, only two single-arm prospective PA series have been published [22,23], and only one prospective cohort study has compared PA with PN [22]. Outcomes data for surveillance are even more scant, and follow-up in surveillance cohorts range only from 12–35 months [18].

Compared with institution-based cohorts, population-based studies can allow comparative assessment of much larger samples of prospectively gathered data. Population-based studies may also have greater external validity than studies of data collected from single or several institutions [24]. In the absence of a very large randomized trial, observational studies of prospectively acquired population-level data may be the best source of information on the comparative effectiveness of T1a renal cancer treatment strategies [13]. Our objective was to compare survival and complication rates associated with PA, PN and RN for T1a RCC in a population-based cohort of older adults.

METHODS

Data source.

Our data source was the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked with Medicare claims. For all incident cancers in their coverage areas, the SEER registries collect information regarding site and extent of disease, the first type of cancer-directed therapy, sociodemographic characteristics, and date and cause of death [25]. The SEER registry is considered an accurate representation of the cancer population in the United States [26]. The Medicare claims files data reflect the near complete capture of health care services for U.S. citizens age 65 and older across all care settings [27]. The SEER-Medicare files link Medicare data from beneficiaries diagnosed with cancer in SEER regions with data from their SEER records. This study was deemed exempt research by the Memorial Sloan Kettering Cancer Center institutional review board. The SEER-Medicare files were used in accordance with a data use agreement with the National Cancer Institute.

Cohort.

We identified patients diagnosed with a first primary RCC between January 1, 2006 and December 31, 2011. The cohort was restricted to patients 66 years or older at diagnosis with a primary tumor less than 4 cm, corresponding to TNM stage T1a. Patients were excluded who had metastatic disease, missing month of diagnosis, or RCC diagnosis only at the time of death. Patients who had a claim for chemotherapy or radiation within the first 12 months

after diagnosis were also excluded. Additionally, we excluded patients enrolled in managed care and those with discontinuous or incomplete Medicare coverage during the study period.

Treatments.

The study cohort was limited to patients who received PA, PN or RN identified in Medicare claims in the 6 months following a clinical diagnosis of kidney cancer (Appendix A). Primary treatment was defined as the first procedure identified after diagnosis. If a patient had claims for PN and RN on the same day, PN was considered the primary treatment, under the assumption that the patient had intra-operative conversion to RN. To specifically study PA in newly diagnosed T1a RCC, we excluded patients who had a claim for open, laparoscopic or unspecified surgical ablation or excision of a kidney lesion prior to or on the same day as their primary procedures (n=215). Two hundred-five of these excluded patients were treated prior to PA, PN or RN. Ten received one of these other procedures on the same day as a primary study procedure; of those, none had PA, 4 had PN and 6 had RN. Patients with a claim for PA, PN or RN subsequent to a claim for RN were also excluded (n=17).

Covariates.

Demographic characteristics included age at diagnosis, sex, race, marital status, urban vs. rural residence, geographic region, median income in the census tract of residence, and prior history of a nonrenal cancer. Tumor characteristics included size and tumor grade. The Romano modification of the Charlson Comorbidity Index, based on inpatient and outpatient claims in the year before primary kidney cancer treatment, was used as a summary measure of comorbidity burden [28,29]. Based on a validated algorithm [30], we also identified specific medical conditions present in the year before primary treatment using diagnoses from inpatient claims, or diagnoses occurring on at least two different outpatient or physician claims more than 30 days apart (Appendix B). These were categorized as cardiovascular conditions (including cardiovascular disease, cerebrovascular disease, peripheral vascular disease and congestive heart failure), renal insufficiency, and diabetes.

Outcomes.

RCC-specific survival was estimated by attributing deaths to RCC as reported in the state death certificate, with follow-up through 2012. Overall survival was estimated with follow-up through 2013.

Complications after primary treatment were identified by procedure codes obtained from inpatient, outpatient and physician claims and by diagnosis codes from inpatient claims or emergency room (ER) visits (Appendix C). Short-term complications, within 30 days of primary procedure, were categorized as cerebrovascular, cardiovascular and peripheral-arterial events; acute renal failure or pyelonephritis; structural renal complications; and non-urological complications (e.g. pneumonia or deep vein thrombosis). In order to minimize misclassification of comorbid conditions as periprocedural complications, we excluded cerebrovascular and cardiovascular diagnosis codes billed during the index admission if the codes were not specific for acute events, such as cardiac dysrhythmias and congestive heart failure. We also excluded 6 codes for minor urologic procedures (Appendix D), such as ureteral stent placement, when billed within 7 days of the primary intervention, since these

additional interventions could be considered normal adjunct procedures sometimes performed with either PA or PN but possibly billed separately.

Long-term non-oncologic outcomes, defined as within 365 days of primary procedure, were categorized as cardiovascular complications, structural kidney complications or renal insufficiency. Because perioperative acute renal failure usually resolves, long-term renal insufficiency was defined by claims submitted between 31 and 365 days following primary treatment. Claims-based definitions of renal insufficiency and other complications were based on previously published methods [31–35]. We also evaluated frequencies of additional RCC-directed procedures after the primary oncologic intervention.

Analysis.

We examined differences in the distribution of patient characteristics by primary treatment. PA was compared with PN and, separately, with RN. Unadjusted associations were evaluated with chi-square tests.

We used propensity score methods to minimize bias related to nonrandom assignment of treatment [36,37]. Propensity scores were estimated in multivariable logistic regression models where the dependent variable was primary procedure (PA vs. PN or vs. RN, modeled separately). The independent variables for the propensity score model were all available patient and disease characteristics, excluding tumor grade. Tumor grade was excluded since in standard clinical practice, tumor grade is usually unknown at the time treatment decisions are made. Propensity scores were used to create stabilized inverse probability of treatment weights (IPTW) for each comparison group (PA vs. PN and PA vs. RN) [38,39]. Covariate balance between treatment groups was examined by standardized difference, with <0.10 considered balanced [40,41].

We used IPTW Cox proportional hazards models with a time-dependent treatment variable to estimate the effect of procedure type on RCC-specific and overall survival, adjusted for unbalanced covariates. The time-dependent treatment variable reflected the most recent cancer-directed procedure − primary treatment or a subsequent procedure − at each event time. We accounted for the lack of independence between patients treated at the same institution by clustering on provider, as defined on the inpatient claim or institutional outpatient claim for the primary procedure. For patients with only a physician claim for the primary procedure (n=82), we identified the most commonly visited institutional provider during the same year as the primary procedure for RCC treatment. The Cox models were also used to generate 1, 3, and 5-year adjusted overall and RCC-specific survival probabilities for each treatment group.

Unadjusted complication rates and 95% confidence intervals for each treatment group were estimated in a time-to-event framework using the Kaplan-Meier method and censoring patients at death or end of follow-up. In all analyses, the time origin was date of the primary procedure and observations were censored at the end of follow-up.

We performed three sensitivity analyses. First, to account for the possibility that survival results may have been biased by an erroneous diagnosis of RCC in tumors that were not

biopsied, we performed a sensitivity analyses of outcomes excluding patients who did not have histologic confirmation of malignancy. Second, because tumor grade was unknown in 57, 36 and 11% of PA, PN and RN patients, respectively, and other factors, such as functional status, are not recorded in SEER-Medicare data at all, we also performed a sensitivity analysis to evaluate the potential impact on the survival hazard ratios associated with PA of an unmeasured binary confounder [42]. Finally, in order to maintain cohort definitions in our complications analysis consistent with those used in the propensity score model and survival analyses, we categorized patients receiving both PN and RN in the same day as having received PN. We therefore also performed a sensitivity analysis of complications in which these patients were instead considered RN patients.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 13.0 (StataCorp, College Station, TX).

Role of the funding source.

Primary research funding and salary support were provided by a grant from the Association of University Radiologists' GE Radiology Research Academic Fellowship (GERRAF). Supplemental funding for statistical analysis was provided by a grant from the Society of Interventional Radiology (SIR) Foundation. No funding source nor any device manufacturer had any input into methodology, authorship decisions or the decision to submit the manuscript for publication. This research was performed in partial fulfillment of requirements for the Master's Degree in Clinical and Translational Research from the Clinical and Translational Science Center of Weill Cornell Medicine, NIH grant UL1 TR000457.

RESULTS

Baseline cohort characteristics.

There were 4,310 patients in the entire cohort, of whom 456 (11%), 1,748 (40%) and 2,106 (49%) were treated primarily with PA, PN and RN, respectively (Table 1). Over time, PA and PN constituted an increasing proportion of primary procedures, while the use of RN decreased. In unadjusted analysis, patients who had PA as their primary procedure were older and sicker than those who had PN or RN, with higher rates of baseline renal insufficiency and cardiovascular disease. Differences in these baseline characteristics were greater between PA and PN patients than between PA and RN patients.

Inverse Probability of Treatment (IPT) weighted cohort characteristics.

Covariate balance ($|d|<0.1$) was achieved for all included variables except year of diagnosis (Appendix E), which was included as a covariate in subsequent adjusted IPTW analyses. This lack of balance was likely due to the low frequency of PA among patients diagnosed prior to 2009. In sub-analyses limited to patients diagnosed from 2009–2011, when PA use was more common, covariate balance for year of diagnosis was achieved (Appendix F).

Survival outcomes.

Median follow-up for the whole cohort was 52 months for overall survival and 42 months for RCC-specific survival. Median follow-up for PA, PN and RN patients was 44, 51 and 55 months, respectively, for overall survival and 33, 40 and 46 months for RCC-specific survival. PA patients had shorter 5-year overall survival than PN patients, 77 (95% CI 74–81) vs. 86% (84–88), but RCC-specific survival between the groups was similar, 95 (93–98) vs. 98% (96–99) (Table 2). Five-year overall and RCC-specific survival were also both similar between PA and RN groups: 74 (71–78) vs. 75% (73–77) and 96 (94–98) vs. 95% (93–96).

PA patients had greater all-cause risk of death throughout follow-up vs. PN patients (adjusted hazard ratio 1.93, 95% CI 1.50–2.49, $p<0.0001$). Differences in cumulative risk of RCC-specific mortality throughout follow-up were suggested by minimally overlapping confidence intervals, though these differences failed to reach statistical significance (AHR 1.99, 0.96–4.14, 0.0652) (Table 3). Risks of both all cause and kidney RCC-specific mortality were similar between PA and RN patients: all cause AHR 0.73, 95% CI 0.43–1.25, $p=0.2537$; and RCC-specific AHR 1.12, 0.92–1.35, 0.2524.

We performed a subanalysis of survival for patients diagnosed from 2009–2011, in which balance was achieved for all covariates (Appendix F). There were 135 (30%), 773 (44%) and 1231 (58%) fewer PA, PN and RN patients included in this subanalysis. Results had broader confidence intervals but were otherwise the same as our primary analysis (Appendix G).

Complications and additional oncologic interventions.

The estimated cumulative 30-day non-urological complication rate for PA patients was 6% (95% CI 4–9), versus 29% (27–30) and 30% (28–32) for PN and RN patients respectively (Table 4). PA patients also had lower rates of acute renal failure than PN or RN patients: <3% vs. 7 (6–9) and 11% (9–12). Rates of cardiovascular complications were low for all treatment groups: 5, 7 and 8% for PA, PN and RN, respectively. Cumulative complication rates through 365 days were also similar between groups, with the exception of 31–365-day cumulative renal insufficiency, which was lower with PA and PN (11 and 9%) than with RN 18%.

One hundred seventy-six PN patients (10%) received RN on the same day as PN, consistent with intra-operative conversion. Excluding same-day PN-to-RN conversions, rates of subsequent RCC interventions within 30 days of PN were <3%. No patients received PN or RN on the same day or within 30 days after PA. The rate of subsequent RCC intervention through 365 days was greater after PA than PN: 7 (95% CI 4–9) vs. < 3% (Table 4). Amongst PA patients receiving additional interventions, 90%, <3% and 8% received PA, PN or RN, respectively. Amongst PN patients receiving additional interventions, <3%, 70% and 29% received PA, PN or RN, respectively.

A subanalysis of complication rates by treatment group was performed for those diagnosed form 2009–2011 using IPTW Kaplan-Meier estimates. As with the survival subanalysis, confidence intervals were broad but resembled the findings of the primary complications analysis (Appendix G).

Sensitivity analyses.

Eighty PA patients (18%), 11 PN patients (1%), and <11 RN patients (<3%) lacked histological confirmation of malignancy. A survival sensitivity analysis was performed excluding these patients (Appendix H). Five-year overall and RCC-specific survival after PA and PN were 75 (95% CI 71–79) vs. 87% (95% CI 85–89) and 94 (92–98) vs. 98% (96–99). These findings resembled those of the primary analysis. Five-year overall and RCC-specific survival comparing PA and RN were 69 (66–73) vs. 76% (74–78) and 94 (92–97) vs. 94% (93–96). The finding of similar RCC-specific survival between PA and RN resembled that of the primary analysis. The finding of longer overall survival with RN differed from the primary analysis.

Although we did not detect a difference in RCC-specific 5-year survival between PA and PN patients in this sensitivity analysis, PA patients did have a higher risk of RCC-specific mortality throughout follow-up compared to PN patients: AHR 2.46, 95% CI 1.21–4.99, p=0.0125 (Appendix H). As with the primary analysis, risk of all-cause mortality was also greater after PA than PN: 2.28, 1.76–2.96, <0.0001. PA patients' risk of RCC-specific mortality remained similar to that of RN patients, while their all-cause risk of death was slightly higher: AHR 0.82, 95% CI 0.49–1.38, p=0.4532; and 1.24, 1.02–1.50, and 0.0311, respectively.

Unidentified confounder sensitivity analysis results suggest it is unlikely a single missing or omitted binary confounder would account for the similarities in oncologic outcomes. For example, if the omitted characteristic were present in 10% of PA patients and 40% of PN patients, and associated with a 50% increase in RCC-specific mortality, then the hazard ratio for RCC-specific mortality after PA vs. PN would increase to 2.27 and be statistically significant (CI 1.10–4.74). However, if an unmeasured confounder were more prevalent in PA patients than PN patients and associated with a 10%−300% increase RCC-specific mortality, the adjusted hazard ratio for PA consistently failed to achieve statistical significance. These results suggest an omitted binary confounder associated with increased RCC-specific mortality would only explain the observed findings if it were more prevalent in the PN group than the PA group.

Comparing PA and RN, if an omitted confounder were present in 70% of PA patients and 10% of RN patients, and associated with a 50% increase in RCC-specific mortality, then the adjusted hazard ratio for PA would decrease to 0.57 and be statistically significant in favor of PA (CI 0.33–0.97). For PA to increase the risk of RCC-specific death compared with RN, an omitted confounder would have to affect 10% of PA patients and 90% of RN patients, and be associated with a 300% increase in RCC-specific mortality. This scenario would yield a hazard ratio for PA of 1.70 (CI 1.01–2.92).

Results of our complications sensitivity analysis categorizing same-day PN-RN patients as RN patients were essentially identical to those of our primary analysis (Appendix H).

CONCLUSIONS

Our study found similar 5-year RCC-specific survival, fewer complications and less long-term renal insufficiency after PA compared to RN. Comparing PA with PN, we found similar 5-year RCC-specific survival and fewer peri-operative complications. This study is concordant with and raises the level of evidence from existing mostly single-center and retrospective studies of renal PA. Four recent larger single center studies with sample sizes ranging from 208–1424 patients reported 5-year post-ablation survival outcomes approaching or equal to those achieved with surgery [22,23,43,44]. But three of these studies were uncontrolled, one was retrospective and one included patients treated laparoscopically as well as percutaneously.

We believe this is the first population level comparative study of PA vs. PN or RN. Two population-level studies, published in 2011 and 2012, compared laparoscopic ablation with surgery [45,46]. The first of these had 1.8 year median follow-up and included stage T1b lesions, tumors 4–7 cm, which are often considered too large for PA or PN [45]. The second study had median follow-up in the ablation group of 1.6 years and was criticized as being at serious risk of selection bias, with healthier patients in the PN group [18,46]. Neither study evaluated peri-operative harms.

The management strategy associated with the fewest peri-operative harms is no treatment at all. Comparative studies of primary imaging surveillance or non-intervention for T1a RCC are fewer and have shorter follow-up than those of PA, PN and RN [18]; however, there is growing consensus that primary non-intervention may be the most appropriate management strategy for patients with the most limited life expectancies, most comorbidities and smallest renal masses [5]. A recent meta-analysis commissioned by the Agency for Healthcare Research and Quality (AHRQ) including RN, PN, PA and surveillance found median 5-year RCC-specific survival for stage T1a RCC patients approaching 95% regardless of management type [18]. The authors concluded:

> “Given the largely equivalent oncologic outcomes, consideration of secondary endpoints including renal functional outcomes, quality of life, perioperative outcomes, and harms are essential in choosing a management strategy for a given patient [18].”

Renal function declines with age, and decreased renal function is independently associated with increased risk of death in a dose-dependent fashion [15]. While some older patients with localized RCC may be best managed with surveillance, 90% of those who do receive treatment will get surgery, and older patients are paradoxically more likely to receive RN than the more technically complex PN [9,10,13]. Supporting PA’s role as a nephron-sparing alternative to PN, we found lower cumulative rates of renal insufficiency requiring emergency department or hospital admission 31–365 days after PA (11%) than after RN (18%). Our findings of favorable renal functional preservation with PA concur with those of the aforementioned meta-analyses of institutional ablation studies and with one 5-way population-level analysis of laparoscopic ablation, PN, RN, open PN and open RN [18,21,47].

We also found markedly lower rates of 30-day non-urologic complications after PA (6%) than after PN (29%) or RN (30%). This low rate resembles rates found by institutional PA studies [21,23]. Our non-urologic post-RN complication rates were similar to those found by a prior SEER-Medicare study [48]. We found about half as many non-urologic complications in PN and RN groups as did the authors of the prior 5-way population-level study of laparoscopic ablation, PN or RN, open PN, and open RN [47]. Since we limited our definition of complications to codes billed as part of emergency department or hospital admissions, it's possible that the rates found by the prior 5-way study reflected less severe complications. Our rates of 30-day non-urological complications associated with percutaneous ablation were substantially lower than those associated with laparoscopic ablation in the prior 5-way population study (6% vs. 40%) [47]. This difference may likely also be due in part to a more stringent definition of complications in our study, but such a marked difference may additionally reflect a real improvement in the safety of ablation from a percutaneous image-guided, rather than laparoscopic, approach. This stands to reason, considering PA is performed with cross-sectional image guidance through sub-centimeter incisions, without peritoneal insufflation and often without general anesthesia. The AHRQ meta-analysis also found generally fewer perioperative harms with ablation and RN than with PN [18]. Our study, specific to PA, provides population-level evidence of a large peri-operative harm reduction with PA compared to either PN or RN.

Limitations.

Our study has several important limitations. Chief among these is the lack of data for patients under age 66. Since the median age at diagnosis of renal cancer is 64 years, our findings are likely less applicable to the younger half of the T1a RCC population.

Another important limitation is data missingness among the included cohort. Eighteen percent of patients and <3% of PN and RN cohorts lacked histologic proof of malignancy. Our sensitivity analysis of histologically-confirmed malignant T1a RCC detected an increased risk of RCC-specific mortality throughout follow-up comparing PA vs. PN (AHR 2.46). However, histologically-confirmed 5-year RCC-specific survival was similar after PA vs. PN: 94 (95% CI 92–98) vs. 98% (95% CI: 96–99). Additionally, we found both similar risk of RCC-specific mortality and similar 5-year RCC-specific survival among histologically-confirmed PA vs. RN patients. Given this similarity between PA and RN, the difference in RCC-specific risk of death we find after PA vs. PN may reflect residual confounding by more favorable baseline characteristics in PN patients, as has been previously described for overall survival in SEER-Medicare studies of PN [18,49]. Our unidentified confounder analysis suggested no single confounding variable was missing from this study. However, despite our efforts, our results could still be somewhat confounded by the sum of several factors that may influence survival.

One such factor is tumor grade. Tumor grade information was missing for most PA patients, preventing its inclusion as a covariate. This is a limitation of our study; however, ignorance of tumor grade at the time of treatment reflects current standard clinical practice. Same-visit needle core biopsy immediately prior to PA has become standard of care in order to inform an appropriate follow-up regimen. Time-of-biopsy preliminary interpretation of needle cores

is inaccurate, and separate-session biopsy to inform treatment type is still an uncommon practice [5, 50]. A discussion of the role of planning biopsy is beyond the scope of the current work, but since the decision to pursue a given treatment in clinical practice is routinely not informed by pathology, we do not expect lack of tumor grade to have contributed substantially to selection bias in the current study.

Similarly SEER-Medicare does not contain information on tumor location. A tumor's location within the kidney impacts the complexity of PA and PN [12], and its proximity to other organs can increase the complexity of PA. These factors play a role in patient selection but cannot be accounted for in our data.

An additional important limitation is our inability to capture results from procedures performed after 2011. The National Cancer Institute's process of linking and validating the separate patient-specific SEER and Medicare data files results in a routine delay in release of the linked data beyond that already experienced with the separate SEER and Medicare data files. Because the technologies used in RN, PN and PA continue to evolve, the safety and effectiveness of all of these procedures, but especially those of PN and PA, are likely to improve over time [9,51]. How they vary over time with respect to each other is uncertain. Since rates of PA increased substantially between 2006 and 2009, we performed subanalyses including year of procedure in our propensity score weighting for patients treated from 2009–2011, the results supported the findings of our primary analysis. Although we cannot exclude the possibility that outcomes achieved by PA, PN or RN with respect to each other have substantially changed since 2011, it is reassuring that our findings resemble those of the most recent institutional studies.

Similarly, to maximize sample size in each cohort, we did not differentiate between robotic and laparoscopic approaches or between radiofrequency, cryo- and microwave ablation. It is known that the different ablation modalities have some different characteristics, such as higher risk of hemorrhage and capacity to treat larger tumors with cryoablation than radiofrequency ablation [52]. However, a 2012 meta-analysis of 883 cases from 31 series did not detect a difference in efficacy or complication rates between cryoablation and radiofrequency ablation [53]. While combining sub-types of PA and open and minimally-invasive surgical approaches within their respective treatment groups may potentially broaden the variance in outcomes within our treatment groups, this within-group heterogeneity is likely small in comparison to the differences between PA, PN and RN.

In conclusion, our findings suggest that, allowing for infrequent re-treatment, appropriately selected older patients with stage T1a renal cancer may expect similar oncologic outcomes, fewer complications and less chronic renal insufficiency after PA vs. RN. This study also suggests that appropriately selected older patients treated with PA may expect oncologic outcomes that approach those of PN while sustaining fewer complications. This first population-level study of PA strengthens the findings of recent institutional studies and raises the level of evidence in support of PA for well-selected older patients with small renal cancers.

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APPENDICES

Appendix A. Primary intervention CPT and ICD-9 codes

PERCUTANEOUS ABLATION

ICD-9 procedure codes: 55.33

CPT codes: 50592, 50593

PARTIAL NEPHRECTOMY

ICD-9 procedure codes: 55.4

CPT codes: 50240, 50543

RADICAL NEPHRECTOMY

ICD-9 procedure codes: 55.51, 55.52, 55.53, 55.54

CPT codes: 50220, 50225, 50230, 50545, 50546

Appendix B. Comorbidity codes

DIABETES

ICD-9 diagnosis codes: 250.0–250.9, 362.0–362.1, 357.2, 366.41

RENAL INSUFFICIENCY

ICD-9 diagnosis codes: 582.X, 583.X, 585.X, 586.X, 588.X, V42.0, V45.11, V56.X

(X = all codes in category indicated by numbers before decimal, e.g.. 582.X = 582.0, 582.1, 582.3, 582.4 … 582.99)

ICD-9 diagnosis codes: 410.X, 412.X

ICD-9 diagnosis codes: 402.01, 402.11, 402.91, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.X, 428.X

ICD-9 diagnosis codes: 430.X, 431.X, 432.X, 433.X, 434.X, 435.X, 436.X, 437.X, 438.X

ICD-9 diagnosis codes: 440.X, 441.X, 442.X, 443.1, 443.8X, 443.9, 447.1

Appendix C. Complication codes

30-DAY NON-UROLOGICAL COMPLICATION CODES

ICD-9 Diagnosis codes: Noncardiogenic shock 785.50, 785.52

Noncardiogenic postoperative shock 998.00, 998.02, 998.09

Pulmonary embolism and infarction, excluding chronic 415.1, 415.11, 415.12, 415.13, 415.19

Cava, cerebral, portal & peripheral DVT 451.11, 451.19, 451.2, 451.81, 451,83, 451.84, 451.89, 451.9, 453.2, 453.40, 453.41, 453.42, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9, 902.10, 902.11, 902.33, 902.34, 902.39, 325, 437.6, 452

Pneumonia 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.42, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487.0, 488.01, 488.11, 488.81, 485, 486

Empyema 510.0, 510.9

Respiratory failure 581.51, 518.52, 518.53, 518.7, 518.81, 518.82, 786.09, 518.84

Peritoneal and retroperitoneal abscess, infection, peritonitis, postoperative infection, infected seroma and wound, wound dehiscence and nonhealing 567.0, 567.21, 567.22, 567.29, 567.3, 567.31, 567.38, 567.39, 567.81, 567.89, 567.9, 569.5, 998.30, 998.51, 998.59, 998.6 (fistula), 998.83

Hematoma or hemorrhage complicating a procedure 998.12, 998.11, 459.0

Foreign body left during a procedure and reaction to retained FB 998.4, 998.7

Hernia of abdominal cavity, intestinal obstruction, impaction and ileus, peritoneal adhesions, Intussusception 551.20, 551.21, 551.29, 551.3, 551.8, 551.9, 552.20, 552.21, 552.29, 553.20, 553.21, 553.29, 560.1, 560.3, 560.89, 560.9, 568.0, 560.89, 560.9, 560.0, 560.1, 560.2, 560.30, 560.32, 560.39, 560.81, 560.89

Laceration or injury of internal organ, or anastomosis, including fistula 569.81, 569.83, 998.6, 863.20, 863.21, 863.29, 863.30, 863.31, 863.39, 863.40, 863.41, 863.42, 836.43, 863.44, 863.45, 863.46, 863.49, 863.50, 863.51, 863.52, 863.53, 863.54, 863.55, 863.56, 863.59, 863.80, 836.85, 863.89, 863.90, 863.99, 998.2, 998.31, 864.02, 864.03, 864.04, 864.05, 864.12, 864.13, 864.14, 864.15, 576.3, 576.4, 868.02, 865.02, 865.03, 865.04, 865.09, 865.12, 865.13, 865.14, 865.19, 863.81, 863.82, 863.83, 863.84, 863.91, 863.92, 863.93, 863.94

Abdominal vascular injury 557.0, 997.71, 444.89, 444.9, 445.89, 447.1, 447.2 453.9, 902.0, 902.10, 902.11, 902.19, 902.20, 902.21, 902.22, 902.23, 902.24, 902.25, 902.26, 902.27, 902.29, 902.31, 902.32, 902.33, 902.34, 902.39, 902.50, 902.51, 902.52, 902.53, 902.54, 902.55, 902.56, 902.59, 902.81, 902, 82, 902.87, 902.89, 902.9

Pneumothorax and air leak 512.0, 512.1, 512.2, 512.8, 512.82, 512.83, 512.84, 512.89

Rhabdomyolysis 728.88

Neuralgia, neuritis and radiculitis, NOS* 729.2

ICD-9 Procedure codes: Organ laceration, resection, ostomy, repair, drainage 46.71, 46.73, 46.79, 46.75, 45.31, 45.33, 45.41, 45.61, 45.62, 45.91, 45.93, 45.94, 46.10, 46.11, 46.13, 46.03, 46.01, 46.03, 46.20, 46.21, 46.22, 46.39, 50.0, 50.61, 50.69, 87.51, 41.43, 41.5, 41.42, 41.95, 52.95

Repair of arterial and venous injury or thrombosis 38.04, 38.06, 38.07, 38.08, 38.09, 38.34, 38.36, 38.37, 38.44, 38.46, 38.47, 39.51, 39.52, 38.64, 38.66, 38.93, 39.25, 39.26; 39.30, 39.31, 39.32, 39.51, 39.52, 39.56, 39.57, 39.58, 39.59, 39.78, 39.98

Pneumothorax requiring chest tube placement 34.04

Drainage of fluid collection, exploration, washout, debridement 50.91, 51.01, 54.91, 54.19, 54.0, 54.95, 54.25, 54.12, 86.22

Repair of incisional hernia 53.51, 53.59, 53.61, 53.62, 53.63, 53.69

CPT codes: Organ laceration, resection, ostomy, repair, drainage 44602, 44603, 44604, 44605, 44110, 44111, 44120, 44121, 44125, 44130, 44310, 44316, 44320, 47350, 47360, 47361, 47362, 75980, 75982, 38100, 38101, 38102, 38120, 38115, 38129, 48545

Repair of venous injury or thrombosis 34151, 34201, 34203, 34401, 34421, 34451, 34841, 34842, 34843, 34844, 34845, 34846, 34847, 34848, 35081, 35082, 35091, 35092, 35111, 35112, 35121, 35122, 35221, 35251, 35281, 35531, 35631, 35537, 35538, 35539, 35540, 35565, 35583, 35585, 35637, 35638, 35646, 35647, 35656, 35665, 35721, 35741, 35840, 35860, 37187, 37188, 37242, 37244, 37212, 75894, 75896, 75966, 75968

Pneumothorax requiring chest tube placement 32551

Drainage of fluid collection, exploration, washout, debridement 47011, 49021, 49041, 49061, 49405, 49406, 49407, 50021, 49020, 49040, 49060, 49062, 49082, 49083, 49000, 49002, 49010, 49084, 11000, 11001, 11005, 11006

Repair of incisional hernia 49560, 49561, 49565, 49566, 49568

CEREBROVASCULAR/CARDIOVASCULAR EVENT CODES

ICD-9 diagnosis codes: 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.81, 411.89, 785.51, 998.01, 430, 431, 432.0, 432.1, 432.9, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 443.21, 443.24, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 444, 447.0

ICD-9 procedure codes: 00.66, 36.09, 36.04, 39.65, 39.66, 37.61, 37.60, 37.62, 37.65, 37.66, 37.68, 99.6, 99.60, 99.61, 99.62, 99.63, 99.64, 99.69, 37.34, 37.71, 37.72, 37.73, 37.75, 37.76, 37.95, 37.97, 37.99, 99.10, 38.81, 38.82, 39.75, 39.76, 38.10, 38.11, 38.12, 38.13, 38.15, 38.18, 38.32, 38.33, 38.38, 38.40, 38.42, 38.48, 38.68, 38.3, 38.88, 38.91, 38.98

CPT codes: 92941, 92973, 92975, 92977, 33960, 33961, 33967, 33970, 33973, 33975, 33976, 33979, 33990, 33991, 92950, 92953, 92960, 92961, 93650, 93653, 93654, 93655, 93656, 93657, 33215, 33216, 33217, 33218, 33220, 33222, 33223, 33224, 33225, 33226, 33227, 33228, 33229, 33234, 33235, 33236, 33237, 33238, 33240, 33230, 33231, 33241, 33262, 33263, 33264, 33243, 33244, 33249, 33270, 33271, 33273, 37195, 61624, 37184, 37185 37186, 37211, 34001, 34051, 34101, 35875, 35876

ICD-9 diagnosis codes: 590.2, 591, 593.3, 593.4, 593.82, 593.5, 593.81, 443.23, 902.41, 997.72, 445.81, 902.42, 902.40, 902.49, 453.3, 405.01, 405.11, 405.91

ICD-9 procedure codes: 55.01, 55.02, 55.03, 55.11, 55.12, 55.29, 55.92, 56.2, 56.0, 59.09, 57.32, 59.8, 87.74, 87.75, 39.24

CPT codes: 50040, 50045, 50392, 50393, 52332, 52334, 50010, 50020, 55020, 52341, 52342, 52343, 52346, 35560

ICD-9 diagnosis codes: 584.5, 584.6, 584.7, 584.8, 584.9, 586, 572.4, 590.10, 590.11, 590.80, 590.81, 590.9, V45.11, V42.0, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8

ICD-9 procedure codes: 39.95, 39.93, 54.98,

CPT codes: G0257, G8575, S9339, 90935, 90937, 90945, 90947, 90960, 90961, 90962, 90966, 90970, 90999, 36800, 36810, 36815

ICD-9 diagnosis codes: 584.5, 584.6, 584.7, 584.8, 584.9, 590.10, 590.11, 590.80, 590.81, 590.9, 285.21, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 572.4, 585.1, 585.2, 585.3, 585.4, 585.5, 585.9, 585.6, 588.0, 588.1, 588.81, 588.89, 588.9, V42.0, V45.11, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8

ICD-9 procedure codes: 39.27, 39.42, 39.94, 39.95, 39.93, 54.98

CPT codes: 36818, 36819, 36820, 36821, 36825, 36830, 36835, G0257, G8575, S9339, 90935, 90937, 90945, 90947, 90960, 90961, 90962, 90966, 90970, 90999, 36800, 36810, 36815

Appendix D. Adjunct urologic procedure codes not counted as complications within 7 days of primary intervention

CYSTOSCOPIC URETERAL STENT PLACEMENT

ICD-9 procedure: 57.32, 59.8

CPT: 52332, 52334

RETROGRADE OR PERCUTANEOUS PYELOGRAMS: ***ICD-9*** 87.74, 87.75

Appendix E.

Standardized Differences* of Inverse-Probability-of-Treatment-Weighted Cohort by Primary Procedure

	(PA vs PN) *d*	(PA vs RN) *d*
Characteristic		
Age at diagnosis		
66–69	−0.02	−0.07
70–74	−0.01	−0.03
75–79	0.02	0.03
80–84	0.02	0.02
85 and older	0.00	0.08
Sex		
Male	0.02	0.01
Female	−0.02	−0.01
Race		
White	−0.01	−0.05
Black	0.03	0.10
Other/unknown	−0.02	−0.04
Marital status		
Married	0.03	0.03
Not married or unknown	−0.03	−0.03
Income quartile		
1st quartile	−0.03	0.01
2nd quartile	0.03	0.03
3rd quartile	0.00	0.02
4th quartile	0.00	−0.05
Unknown	−0.02	−0.05
Geographic region		
Northeast	−0.07	0.04
West	0.04	−0.07
Midwest	−0.03	0.05
South	0.05	−0.06
Urban vs. rural residence		
Urban	0.04	0.00

	(PA vs PN) *d*	(PA vs RN) *d*
Rural	−0.04	0.00
Tumor size		
<2 cm	−0.01	−0.01
2-<3cm	0.03	−0.02
3-<4cm	−0.02	0.03
Charlson comorbidity score **		
0	−0.02	−0.08
1	−0.01	0.01
2+	0.03	0.07
Prior cancer diagnosis		
Yes	0.01	0.03
No	−0.01	−0.03
Pre-existing conditions **		
Cardiovascular disease		
Yes	0.04	0.07
No	−0.04	−0.07
Diabetes		
Yes	0.04	0.06
No	−0.04	−0.06
Renal insufficiency		
Yes	0.01	0.05
No	−0.01	−0.05
Year of diagnosis		
2006	−0.22	−0.17
2007	−0.03	0.03
2008	0.10	0.07
2009	0.19	0.15
2010	0.06	0.00
2011	−0.16	−0.11

Notes:

PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

* *d*=standardized difference; |*d*|<0.10 for all included covariates except year of diagnosis

** Charlson comorbidity score and pre-existing conditions based on Medicare claims in the year prior to procedure

Appendix F.

Standardized differences * of baseline cohort characteristics by primary procedure after inverse-probability-of-treatment weighting: patients diagnosed 2009–2011

	PA n=321		PN n=975		(PA vs PN)	RN n=875		(PA vs RN)
Characteristic	**N**	**%**	**N**	**%**	***d***	**N**	**%**	***d***
Age at diagnosis								
66–69	58	18%	350	36%	−0.02	225	26%	−0.01

	PA n=321		PN n=975		(PA vs PN)	RN n=875		(PA vs RN)
Characteristic	**N**	**%**	**N**	**%**	***d***	**N**	**%**	***d***
70–74	86	27%	333	34%	0.00	270	31%	−0.03
75–79	73	23%	182	19%	0.02	196	22%	−0.01
80–84	75	23%	97	10%	0.00	118	13%	0.02
85 and older	29	9%	13	1%	−0.01	66	8%	0.05
Sex								
Male	196	61%	586	60%	0.05	432	49%	0.03
Female	125	39%	389	40%	−0.05	443	51%	−0.03
Race								
White	275	86%	829	85%	−0.02	738	84%	−0.05
Black	19	6%	91	9%	0.04	81	9%	0.06
Other/unknown	27	8%	55	6%	−0.02	56	6%	0.00
Marital status								
Married	181	56%	654	67%	0.04	519	59%	−0.03
Not married or unknown	140	44%	321	33%	−0.04	356	41%	0.03
Income quartile								
1st quartile	65	20%	218	22%	−0.06	242	28%	−0.02
2nd quartile	73	23%	247	25%	0.00	229	26%	−0.01
3rd quartile	85	26%	221	23%	0.07	226	26%	0.03
4th quartile	90	28%	283	29%	−0.01	170	19%	0.00
Unknown	8	2%	6	1%	0.00	8	1%	0.00
Geographic region								
Northeast	63	20%	237	24%	−0.04	163	19%	0.01
West	153	48%	351	36%	−0.01	336	38%	0.01
Midwest	53	17%	112	11%	0.00	105	12%	0.01
South	52	16%	275	28%	0.06	271	31%	−0.03
Urban vs. rural residence								
Urban	284	88%	813	83%	0.07	732	84%	0.05
Rural	37	12%	162	17%	−0.07	143	16%	−0.05
Tumor grade								
Low	126	39%	631	65%	−0.55	559	64%	−0.54
High	13	4%	197	20%	−0.55	215	25%	−0.59
Unknown	182	57%	147	15%	1.02	101	12%	1.10
Tumor size								
<2 cm	69	21%	234	24%	0.03	121	14%	0.03
2-<3cm	151	47%	396	41%	0.02	297	34%	0.01
3-<4cm	101	31%	345	35%	−0.05	457	52%	−0.03
Charlson comorbidity score **								
0	123	38%	439	45%	0.04	319	36%	−0.03
1	69	21%	263	27%	−0.03	244	28%	−0.02
2+	129	40%	273	28%	−0.02	312	36%	0.04

	PA n=321		PN n=975		(PA vs PN)	RN n=875		(PA vs RN)
Characteristic	**N**	**%**	**N**	**%**	***d***	**N**	**%**	***d***
Prior cancer diagnosis								
Yes	87	27%	213	22%	0.00	190	22%	0.02
No	234	73%	762	78%	0.00	685	78%	−0.02
Pre-existing conditions **								
Cardiovasular disease								
Yes	101	31%	192	20%	0.00	246	28%	0.03
No	220	69%	783	80%	0.00	629	72%	−0.03
Diabetes								
Yes	112	35%	293	30%	0.00	306	35%	0.01
No	209	65%	682	70%	0.00	569	65%	−0.01
Renal insufficiency								
Yes	62	19%	114	12%	−0.03	142	16%	0.01
No	259	81%	861	88%	0.03	733	84%	−0.01
Year of diagnosis								
2009	112	35%	316	32%	−0.02	333	38%	0.04
2010	109	34%	315	32%	0.03	289	33%	−0.04
2011	100	31%	344	35%	−0.02	253	29%	−0.01

Notes:

PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

* *d*=standardized difference; |*d*|<0.10 for all included covariates

** Charlson comorbidity score and pre-existing conditions based on Medicare claims in the year prior to procedure

Appendix G.

Subanalyses of patients diagnosed 2009–2011 (balanced by year) IPTW-adjusted overall and RCC-specific survival at 1 and 3 years, by treatment type among patients diagnosed 2009–2011.

	PA % (95% CI)	PN % (95% CI)	PA % (95% CI)	RN % (95% CI)
RSS				
1-year	99 (99–100)	100 (99–100)	99 (99–100)	99 (98–99)
3-year	98 (96–100)	99 (98–100)	98 (97–100)	96 (95–98)
OS				
1-year	96 (95–98)	98 (97–98)	95 (93–97)	94 (93–96)
3-year	90 (87–93)	94 (92–95)	87 (84–90)	86 (83–88)

Notes:

-Survival probabilities generated from an Inverse Probability of Treatment-Weighted (IPTW) Cox model with a time-dependent treatment variable

-First two columns give survival probabilities for PA-PN matched cohorts; second two columns give survival probabilities for PA-RN matched cohorts.

-RCC, renal cell carcinoma; RSS, RCC-specific survival; OS, overall survival; PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

-Results are essentially the same as those from primary analysis

IPTW-adjusted impact of treatment type on risk of RCC-specific death and death from any cause among patients diagnosed 2009–2011.

	PA vs. PN		PA vs. RN	
	AHR (95% CI)	***p***	**AHR (95% CI)**	***p***
RCC-specific mortality Cox model	1.47 (0.47–4.576)	0.80	0.36 (0.129–1.02)	0.15
All-cause mortality Cox model	1.82 (1.25–2.66)	0.005	0.88 (0.65–1.19)	0.70

Notes:

-Impact of percutaneous ablation versus PN or RN on risk of overall and RCC-specific mortality

Inverse-Probability of Treatment-Weighted (IPTW) Cox model clustered on institutional provider; observation censored at end of follow-up, treatment type is a time-dependent variable

-RCC, renal cell carcinoma; AHR: adjusted hazard ratio

-Except for the increased similarity of RCC-specific mortality between PA and PN, results resemble those of the primary analysis.

IPTW-adjusted complication rates by primary procedure 2009–2011

Adverse event	**PA (n=321) % (95% CI)**	**PN (n=975) % (95% CI)**		**PA (n=321) % (95% CI)**	**RN (n=875) % (95% CI)**
In 30 days					
Non-urological	12% (9–14)	25% (22–27)		12% (10–15)	27% (24–29)
Cardiovascular *	7% (5–9)	5% (4–6)		7% (5–9)	7% (5–8)
Acute renal failure	5 (3–6)	7% (5–8)		6% (4–8)	12% (10–14)
Structural kidney	<3%	3%		<3%	<3%
Subsequent RCC-directed procedures	<3%	<3%		<3%	N/A
In 365 days					
Cardiovascular	21% (17–24)	16% (14–18)		24% (20–29)	22% (19–25)
Structural kidney	3% (2–5)	6% (4–7)		4% (2–6)	4% (3–5)
Subsequent RCC-directed procedures	4% (3–6)	<3%		4 (2–6)	N/A
From 31–365 days					
Renal insufficiency	11% (8–14)	9% (7–11)		14% (10–17)	21% (17–24)

Notes:

-Survival probabilities generated from an inverse probability of treatment-weighted (IPTW) cox model with a time-dependent treatment variable

-First two columns give survival probabilities for PA-PN IPTW cohorts; second two columns give survival probabilities for PA-RN IPTW cohorts.

-RCC, renal cell carcinoma; RSS, RCC-specific survival; OS, overall survival; PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

-Except longer 5-year OS after RN vs. PA, findings are similar to those from the primary analysis.

Appendix H.

Sensitivity analyses IPTW-adjusted overall and RCC-specific survival at 1, 3, and 5 years, by treatment type in histologically-confirmed patients

	PA % (95% CI)	PN % (95% CI)	PA % (95% CI)	RN % (95% CI)
RSS				
1-year	99 (98–100)	99 (99–100)	99 (98–99)	99 (98–99)
3-year	97 (96–99)	99 (98–99)	97 (95–98)	97 (96–98)
5-year	94 (92–98)	98 (96–99)	94 (92–97)	94 (93–96)
OS				
1-year	95 (94–97)	98 (97–98)	94 (92–95)	95 (94–96)
3-year	88 (85–90)	94 (93–95)	82 (80–85)	86 (85–88)
5-year	75 (71–79)	87 (85–89)	69 (66–73)	76 (74–78)

Notes:

-First two columns give survival probabilities for PA-PN matched cohorts; second two columns give survival probabilities for PA-RN matched cohorts.

-Survival probabilities generated from an Inverse Probability of Treatment-Weighted (IPTW) Cox model with a time-dependent treatment variable

-Results are essentially the same as those from primary analysis

-RCC, renal cell carcinoma; RSS, RCC-specific survival; OS, overall survival; PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

IPTW-adjusted impact of treatment type on risk of RCC-specific death and death from any cause in patients with histologically-confirmed disease

	PA vs. PN		PA vs. RN	
	AHR (95% CI)	*p*	AHR (95% CI)	*p*
RCC-specific mortality Cox model	2.46 (1.21–4.99)	0.012	0.82 (0.49–1.38)	0.45
All-cause mortality Cox model	2.28 (1.76–2.96)	<0.001	1.24 (1.02–1.50)	0.031

Notes:

-Impact of percutaneous ablation versus PN or RN on risk of overall and RCC-specific mortality

-Inverse Probability of Treatment-Weighted (IPTW) Cox model clustered on institutional provider; observation censored at end of follow-up, treatment type is a time-dependent variable

-RCC, renal cell carcinoma; AHR: adjusted hazard ratio

-Higher risk of RCC-specific mortality with PA vs. PN and of all-cause mortality with PA vs. RN found in this analysis differ from findings of the primary analysis. Similar risk of RCC-specific mortality between PA and RN and higher risk of all-cause mortality with PA vs. PN resemble findings from the primary analysis.

Complications by primary procedure type, categorizing same-day PN-RN as RN

Adverse event	PA (n=456) % (95% CI)	PN (n=1,572) % (95% CI)	RN (n=2,282) % (95% CI)
In 30 days			
Non-urological	6 (4–9)	28 (26–30)	31 (29–32)

Adverse event	PA (n=456) % (95% CI)	PN (n=1,572) % (95% CI)	RN (n=2,282) % (95% CI)
Cardiovascular *	5 (3–7)	7 (6–8)	8 (7–9)
Acute renal failure	<3	7 (6–9)	10 (9–12)
Structural kidney	<3	4 (3–5)	<3
Subsequent RCC-directed procedures	<3	<3	N/A
In 365 days			
Cardiovascular	20 (17–24)	16 (14–18)	21 (19–23)
Structural kidney	4 (3–7)	6 (5–7)	3 (3–4)
Subsequent RCC-directed procedures [b]	7 (4–9)	<3	N/A
From 31–365 days			
Renal insufficiency	11 (8–14)	9 (7–10)	18 (16–19)

Notes:

-PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy; RCC, renal cell carcinoma

-Cell percentages where n <11 not shown, in adherence with SEER-Medicare Data Use Agreement.

-Billing codes to identify complications in Medicare claims are given in Appendix C.

-Event rates are based on Kaplan-Meier estimates and represent the estimated complication rates of the un-weighted cohort.

* As discussed in Appendix I, rates for PN and RN may be underestimated.

As discussed in Appendix I, rates for PN and RN may be underestimated.

As discussed in Appendix I, rates may be underestimated for PN and RN and under- or overestimated for PA.

-Number of patients in each cohort varies from primary analysis due to PN-RN patients being re-defined as RN patients

-Event rates are essentially the same as those found by the primary analysis (table 4).

APPENDIX I – technical notes

i. The estimated frequency of cardiovascular complications within 30 days after PA we found was similar between PA (5%), PN (7%) and RN (8%) treatment groups. Based on institutional literature, the AHRQ meta-analysis found lower rates of cardiovascular complications associated with ablation compared to PN or RN [A]. To avoid confounding baseline comorbidity with complication, we did not include as complications cardiovascular claims during admission for the oncologic intervention if the billing codes did not specify acute events, for example codes for dysrhythmias and congestive heart failure. Since PA is often performed as an outpatient procedure, this methodology may have preferentially captured more cardiovascular complications after PA than after PN or RN, which usually require post-operative hospitalization.

ii. Estimated rates of repeat oncologic intervention through 365 days were greater after PA than PN: 7% (95% CI: 4–9%) vs. < 3%. The rate of repeat intervention for PA in the subanalysis of patients treated from 2009–2011 was lower than in the total cohort: 4% (95% CI: 3–6%). This may reflect improvements in technique during early adoption of PA. Our 7% whole-cohort post-PA re-intervention rate is similar to that reported in somewhat older larger institutional

ablation studies [B,C]. Our 4% post-PA re-intervention rate from 2009–2011 resembles rates found in the most recent institutional series, which report 3-year-post PA recurrence-free survival of 97 and 98% [D,E]. In keeping with the findings of a prior institutional study [F], 90% of our PA patients receiving additional oncologic treatment received additional PA.

Given the indolence of most RCCs, it is probable that we underestimate the true rate of re-intervention after both PA and PN by capturing only those additional procedures performed in the first year post-intervention. We may also underestimate local recurrence rates across treatment groups because some patients may choose to defer additional intervention in favor of surveillance, for which there is no ICD-9 or CPT code. In contrast, our rate of post-PA re-intervention in particular may be overestimated due to enhancement in the ablation bed on early post-treatment imaging surveillance being mistaken for recurrent tumor. It has historically been common to obtain post-ablation CT or MRI 1–3 months after treatment. A study published in 2012 found that suspicious tissue enhancement in the post-ablation bed seen at 3 months follow-up resolved spontaneously in 50% of subsequent scans [G]. A more temporally detailed analysis of re-intervention was beyond the scope of our study.

Appendix I References

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Table 1.

Baseline cohort characteristics by primary procedure (prior to inverse probability of treatment weighting)

	PA n=456	PN n=1,748	(PA vs PN)	RN n=2,106	(PA vs RN)			
Characteristic	**N**	**%**	**N**	**%**	**p-value**	**N**	**%**	**p-value**
Age at diagnosis					<0.001			<0.001
66–69	73	16%	577	33%		506	24%	
70–74	118	26%	598	34%		621	29%	
75–79	108	24%	370	21%		514	24%	
80–84	108	24%	173	10%		325	15%	
85 and older	49	11%	30	2%		140	7%	
Sex					0.78			<0.001
Male	274	60%	1038	59%		1039	49%	
Female	182	40%	710	41%		1067	51%	
Race					0.019			0.015
White	387	85%	1491	85%		1787	85%	
Black	27	6%	149	9%		186	9%	
Other/unknown	42	9%	108	6%		133	6%	
Marital status					<0.001			0.66
Married	260	57%	1176	67%		1224	58%	
Not married or unknown	196	43%	572	33%		882	42%	
Income quartile					0.22			0.007
1st quartile	93	20%	400	23%		564	27%	
2nd quartile	105	23%	405	23%		554	26%	
3rd quartile	120	26%	417	24%		528	25%	
4th quartile	127	28%	505	29%		424	20%	
Unknown	11	2%	21	1%		36	2%	
Geographic region					<0.001			<0.001
Northeast	88	19%	453	26%		439	21%	
West	216	47%	608	35%		780	37%	
Midwest	63	14%	195	11%		259	12%	
South	89	20%	492	28%		628	30%	
Urban vs. rural residence					0.015			0.004
Urban	402	88%	1460	84%		1740	83%	
Rural	54	12%	288	16%		366	17%	
Tumor grade					<0.001			<0.001
Low	179	39%	1142	65%		1402	67%	
High	18	4%	344	20%		468	22%	
Unknown	259	57%	626	36%		236	11%	
Tumor size					0.13			<0.001
<2 cm	91	20%	427	24%		272	13%	
2-<3cm	203	45%	728	42%		742	35%	

	PA n=456	PN n=1,748	(PA vs PN)	RN n=2,106	(PA vs RN)			
Characteristic	**N**	**%**	**N**	**%**	**p-value**	**N**	**%**	**p-value**
3-<4cm	162	36%	593	34%		1092	52%	
Charlson comorbidity score *					<0.001			0.004
0	181	40%	774	44%		829	39%	
1	101	22%	491	28%		609	29%	
2+	174	38%	483	28%		668	32%	
Prior cancer diagnosis					0.037			0.004
Yes	117	26%	369	21%		414	20%	
No	339	74%	1379	79%		1692	80%	
Pre-existing conditions *								
Cardiovascular disease					<0.001			0.014
Yes	143	31%	343	20%		542	26%	
No	313	69%	1405	80%		1564	74%	
Diabetes					0.27			0.67
Yes	150	33%	528	30%		671	32%	
No	306	67%	1220	70%		1435	68%	
Renal insufficiency					<0.001			0.005
Yes	85	19%	195	11%		286	14%	
No	371	81%	1553	89%		1820	86%	
Year of diagnosis					<0.001			<0.001
2006	22	5%	251	14%		425	20%	
2007	40	9%	245	14%		418	20%	
2008	73	16%	277	16%		388	18%	
2009	112	25%	316	18%		333	16%	
2010	109	24%	315	18%		289	14%	
2011	100	22%	344	20%		253	12%	

Notes:

PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

* Charlson comorbidity score and pre-existing conditions based on Medicare claims in the year prior to procedure

Table 2.

IPTW-adjusted overall and RCC-specific survival at 1, 3, and 5 years, by treatment type.

	PA	PN	PA	RN
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
RSS				
1-year	99 (99–100)	99 (99–100)	99 (98–99)	99 (98–99)
3-year	98 (97–99)	99 (98–99)	98 (96–99)	97 (96–98)
5-year	95 (93–98)	98 (96–99)	96 (94–98)	95 (93–96)
OS				
1-year	96 (95–97)	98 (97–98)	95 (94–96)	95 (94–96)
3-year	89 (87–91)	94 (93–95)	85 (83–87)	86 (85–87)
5-year	77 (74–81)	86 (84–88)	74 (71–78)	75 (73–77)

Notes:

-Survival probabilities generated from an inverse probability of treatment-weighted (IPTW) Cox model with a time-dependent treatment variable

-First two columns give survival probabilities for PA-PN IPTW cohorts; second two columns give survival probabilities for PA-RN IPTW cohorts.

-RCC, renal cell carcinoma; RSS, RCC-specific survival; OS, overall survival; PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy

Table 3.

IPTW-adjusted impact of treatment type on risk of RCC-specific death and death from any cause

	PA vs. PN	PA vs. RN		
	AHR (95% CI)	***p***	**AHR (95% CI)**	***p***
RCC-specific mortality Cox model	1.99 (0.96–4.143)	0.06	0.73 (0.43–1.25)	0.25
All-cause mortality Cox model	1.93 (1.50–2.49)	<0.001	1.12 (0.92–1.35)	0.25

Notes:

-Impact of percutaneous ablation versus PN or RN on risk of overall and RCC-specific mortality

-Inverse probability of treatment-weighted (IPTW) Cox model clustered on institutional provider: observation censored at end of follow-up, treatment type is a time-dependent variable

-RCC, renal cell carcinoma; AHR: adjusted hazard ratio

Table 4.

Complication event rate estimates by primary procedure

Adverse event	PA n=456 % (95% CI)	PN n=1,748 % (95% CI)	RN n=2,106 % (95% CI)
In 30 days			
Non-urological	6 (4–9)	29 (27–30)	30 (28–32)
Cardiovascular*	5 (3–7)	7 (6–8)	8 (7–9)
Acute renal failure	<3	7 (6–9)	11 (9–12)
Structural kidney	<3	4 (3–5)	<3
Subsequent RCC-directed procedures	<3	<3	N/A
In 365 days			
Cardiovascular	20 (17–24)	17 (15–18)	21 (19–23)
Structural kidney	4 (3–7)	6 (5–7)	3 (3–4)
Subsequent RCC-directed procedures[b]	7 (4–9)	<3	N/A
From 31–365 days			
Renal insufficiency	11 (8–14)	9 (8–10)	18 (17–20)

Notes:

-PA, percutaneous ablation; PN, partial nephrectomy; RN, radical nephrectomy; RCC, renal cell carcinoma

-Cell percentages where n <11 not shown, in adherence with SEER-Medicare Data Use Agreement.

-Billing codes to identify complications in Medicare claims are given in Appendix C.

-Event rates are based on Kaplan-Meier estimates and represent the estimated complication rates of the un-weighted cohort. In keeping with methods used for propensity score weighting and survival analysis, patients receiving same-day PN and RN are categorized here as having received PN. A sensitivity analysis was performed in which these patients were categorized as having received RN (Appendix H). Results were essentially the same.

*As discussed in Appendix I, rates for PN and RN may be underestimated.

As discussed in Appendix I, rates may be underestimated for PN and RN and under- or overestimated for PA.