Adverse Health Outcomes Associated with Surgical Management of the Small Renal Mass

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Purpose: Partial and radical nephrectomy are treatments for the small renal mass. Partial nephrectomy is considered the gold standard as it may protect against renal dysfunction compared to radical nephrectomy. However, both treatments may cause adverse health outcomes.

Materials and Methods: A matched cohort study was performed using the SEER (Surveillance, Epidemiology and End Results)-Medicare data set. Individuals treated with partial or radical nephrectomy for 4 cm or smaller nonmetastatic renal cell carcinoma were compared to 2 control groups (nonmuscle invasive bladder cancer and noncancer). A greedy algorithm matched surgical groups to controls. Medicare claims were examined for renal, cardiovascular and secondary cancer events.

Results: Patients who underwent partial nephrectomy (1,471) and radical nephrectomy (4,299) were matched to controls. The time to event model demonstrated an increased risk of renal events for both treatments. Compared to the bladder cancer control and noncancer control groups, radical nephrectomy hazard ratios for renal events were 2.415 ($p < 0.0001$) and 6.211 ($p < 0.0001$), respectively, while partial nephrectomy hazard ratios were 1.513 ($p < 0.0001$) and 4.926 ($p < 0.0001$), respectively. Secondary cancers were increased for partial nephrectomy and radical nephrectomy compared to both control groups ($p < 0.0001$). Cardiovascular events were increased for both treatments compared to noncancer controls ($p < 0.0001$), but not compared to bladder cancer controls.

Conclusions: Partial nephrectomy and radical nephrectomy may lead to adverse health outcomes. Compared to controls, partial nephrectomy and radical nephrectomy are associated with worsened renal outcomes. The increase in secondary cancers and cardiovascular events with both treatments is notable, and requires further investigation. Further research should investigate if active surveillance of the appropriately selected small renal mass limits adverse health outcomes.

Key Words: watchful waiting, nephrectomy, kidney neoplasms

Abbreviations and Acronyms

AS = active surveillance
BCC = bladder cancer control
CCI = Charlson comorbidity index
CKD = chronic kidney disease
CSS = cancer specific survival
ESRD = end stage renal disease
HTN = hypertension
NCC = noncancer control
PN = partial nephrectomy
RCC = renal cell carcinoma
RN = radical nephrectomy
SRM = small renal mass

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For other articles on related topics see pages 479 and 487.

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SURGICAL management has been the mainstay of treatment for renal cell carcinoma. Despite an increased incidence of the disease, RCC mortality rates have remained fairly stable.[1,2] These findings led investigators

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to hypothesize that surgery for the small renal mass is often unnecessary. Hollingsworth et al suggested, "the current paradigm for treating kidney cancer is not based on empiricism, and these findings call to question the appropriateness of extirpative surgery in all patients."[2]

Over diagnosis is an increasingly prevalent phenomenon as many patients undergo treatment for cancers that may have remained clinically silent.[3] For prostate cancer the treatment related side effects (impotence and incontinence) are easily recognizable and quantifiable. Adverse health outcomes associated with the treatment of RCC involve long-term consequences from nephron loss as opposed to the immediate impact seen after the treatment of prostate cancer.

The extent of chronic kidney disease has recently been linked to cardiac mortality, which is also believed to be related to loss of renal function after treatment of RCC.[4,5] Because of these concerns, partial nephrectomy expanded to an elective setting.[6] In addition to limiting the removal of normal parenchyma, PN offers an oncologic outcome similar to that of radical nephrectomy.[7,8] Multiple series have demonstrated that compared to RN, PN may protect against CKD and proteinuria.[9–12] CKD may also increase cancer risk, which is a new concern with RCC overtreatment.[13,14]

Recently PN has been labeled the standard of care for the SRM.[15] However, studies comparing PN and RN have demonstrated renal events with both treatments.[9,12] With data emerging on the safety of active surveillance, it is important to understand adverse health outcomes associated with current surgical paradigms.[6] While studies compare RN to PN, to our knowledge none has assessed surgery vs no intervention or AS. Ideally a randomized clinical trial would improve our understanding of the risk/benefit ratio of SRM treatment since AS may also have risks, including anxiety and tumor progression, and those related to frequent imaging.

To better understand the adverse health outcomes associated with surgical management, we conducted a matched cohort study using the SEER-Medicare linkage.[16] We measured cardiovascular, renal and secondary cancer events associated with PN and RN compared to controls.

METHODS

SEER-Medicare was used to identify individuals 66 years old or older diagnosed with RCC from 1992 to 2007 with 2 or more years of followup. As SEER-Medicare claims are available through 2009, this served as the end of followup. Patients with RCC were identified in SEER using ICD-O-3 (International Classification of Diseases for Oncology, 3rd Edition) codes.[12] To exclude nonRCC renal malignancies, only recognizable subtypes were selected. Inpatient Medicare files for ICD-9 (International Classification of Diseases, 9th Revision) claims identified patients treated with PN (55.4) or RN (55.5, 55.51). Cases of bilateral nephrectomy (55.54), or 2 or more surgical claims were excluded from study. We also excluded patients with nodal or metastatic disease at presentation. SRMs were defined as tumors measuring 4 cm or less. No exclusion was used for pathological up staging.

Demographic variables including age, gender, race, region and treatment year were obtained. The inclusion of patients 66 years old or older allowed more than 85% of comorbidities to be captured.[17] Inpatient and outpatient claims were used to calculate CCI.[18] Patients with ESRD at diagnosis were excluded from study.

Differences exist between patients undergoing PN and RN and, therefore, each category was separately matched to controls.[19] Noncancer controls included individuals without a prior cancer chosen from a 5% random sample of Medicare beneficiaries 66 years old or older. To control for nonmeasurable differences in health characteristics and followup practices between cancer and noncancer groups, we selected a separate urological cancer control. Nonmuscle invasive bladder cancer was chosen due to excellent cancer specific survival and similar oncologic surveillance. The bladder cancer controls were selected from SEER-Medicare, and included patients 66 years old or older with low grade (grade 1 or 2) nonmuscle invasive bladder cancer (Ta, T1 and Tis) who did not undergo cystectomy.[20] As different cancers have unique biology, comparisons were performed only for adverse health outcomes assessment.

A greedy algorithm was chosen to match RCC cases to controls. With the greedy algorithm, a randomly treated subject is matched to controls by the closest propensity score based on defined covariates.[21] For surgical groups the controls were matched by age ($\pm$3 years), year of diagnosis, race, gender, CCI and HTN. Hypertension was chosen since it is not represented in the CCI. Year of surgery was used to match NCCs using the first month of Medicare eligibility.

We evaluated claims for cardiovascular, renal and secondary cancer events more than 30 days postoperatively to exclude perioperative complications.[12] We used CKD cardiovascular event coding similar to that used by Go et al.[4] Renal events were coded as in the study by Miller et al, and included dialysis services, ESRD, transplantation, nephrology consultation and ESRD hospitalizations.[12] Secondary cancers were identified using ICD-9 codes, excluding benign tumors. In the RCC and BCC groups the same cancer was excluded as this may represent recurrence. Multiple cancer events were consolidated into a solitary outcome. Claims were evaluated through the end of followup or death. We examined the CSS associated with PN, RN and the BCC group calculated from surgery until death or last followup.

The chi-square test, ANOVA and generalized linear modeling were used to evaluate differences between groups. Kaplan-Meier estimates were performed for time to event and CSS. Differences were calculated using log rank tests. Cox proportional hazard models assessed the