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Survival benefit of partial nephrectomy: Reconciling experimental and observational data

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Abstract

Given recent epidemiological and practice trends, small kidney cancers are poised to become a focus of modern-day surgical care provided by urologists and urologic oncologists. For the past decade, partial nephrectomy has been viewed as preferable to radical nephrectomy for the treatment of many patients with early-stage kidney cancer, partly because observational studies suggest a survival benefit with nephron sparing. More recently, European Organisation for Research and Treatment of Cancer 30904—a phase 3 randomized control trial—demonstrated better survival for patients treated with radical vs. partial nephrectomy. Shortly thereafter, an instrumental variable analysis reported a survival advantage with partial nephrectomy. Although seemingly contradictory, these studies are potentially reconcilable when considering methodological differences and other empiric work.

Keywords: Kidney neoplasm; Nephrectomy; survival

1. Commentary

Surgical decision making often distills down to 2 core considerations: the procedural risk to the patient and the potential benefits of treatment. For patients with clinical category T1a kidney cancer, radical nephrectomy has historically been considered the standard of care [1]. In more recent years, partial nephrectomy—widely considered a more complex operation—has demonstrated equivalent cancer control and better preservation of renal function [2–5]. Several observational studies have also highlighted improved survival among patients treated with partial vs. radical nephrectomy, which has been attributed to the avoidance of chronic kidney disease and subsequent morbidity and mortality [6–10]. Based on these data, nephron sparing has been identified as a priority in the management of patients with small, localized kidney cancer [11]. However, contradictory findings from a randomized controlled trial have led many to question the survival data supporting the broader use of partial nephrectomy [12].

Until now, practice guidelines for localized kidney cancer have drawn almost entirely from retrospective series or population-based registries. Though informative, these observational data remain subject to potential bias. For example, patients selected to undergo partial nephrectomy may be systematically healthier than those treated with radical nephrectomy. However, the matter of selection bias is not a new consideration. Early comparative studies have attempted to address these concerns by matching based on tumor stage and age [5]. More contemporary assessments use modeling to adjust for an ever-wider panel of characteristics [7]. Some investigators have ventured further, using propensity scores to balance measurable covariates [13,14]. Despite these efforts, residual confounding from unmeasured variables can persist and sway analytic output. In fact, a recent analysis of linked Surveillance, Epidemiology, and End Results-Medicare data suggests that patients treated with partial nephrectomy outlive adults without cancer, highlighting the potential influence of selection bias on survival differences noted in observational data sets [15].

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Such biases can be addressed through several mechanisms; the most established and accepted being randomized controlled trials. By assigning treatment at random, potentially within a specified stratum, this experimental design balances both measured and unmeasured covariates to isolate the causal relationship between the study intervention and outcomes. In December 2010, the European Organisation for Research and Treatment of Cancer (EORTC) released the much anticipated survival findings from its randomized, noninferiority trial comparing partial and radical nephrectomy for patients with tumors less than 5 cm in size [12]. Randomization appeared successful, with balance noted across measured covariates in both treatment arms. Contrary to the existing body of clinical research [16], this phase 3 study showed superior survival outcomes for patients treated with radical nephrectomy. In a subgroup of patients with pathologically confirmed kidney cancer, the difference in survival did not reach statistical significance.

Though held as the gold standard for comparative effectiveness research, randomized controlled trials are not impermeable to methodological concerns. These experiments typically apply strict inclusion and exclusion criteria, resulting in highly selected patient cohorts. Over the span of a decade, the EORTC trial enrolled 541 patients from 45 institutions in 17 countries, approximately 1 patient per year per institution. For context, Mayo Clinic, UCLA, and Memorial Sloan Kettering Cancer Center reported treatment of 648, 114, and 252 patients with small kidney tumors, respectively, during similar, overlying periods [6,17,18]. Trials studying new surgical interventions also face unique challenges related to the learning curve, provider variation in technique and patient care, and concern for equipoise [19]. Over the study period, use of partial nephrectomy for patients with clinical category T1a tumors increased from 5%–14% to 20%–42% in the United States, suggesting increasing awareness and comfort with the procedure [20]. Additionally, a multitude of technical modifications has been since described, including evolving time thresholds for ischemia, parenchyma preservation, and minimally invasive surgery [21–23]. Although the trial itself stands as a notable accomplishment and the findings appear internally valid, legitimate concerns surrounding its applicability to current-day practice remain, regarding the patients routinely served and the surgical technique.

In this setting, natural and quasi-experiments can potentially ameliorate issues related to selection bias while also reflecting real-world effectiveness. The Oregon Medicaid Experiment leveraged a state-sponsored lottery that randomly awarded households the opportunity to apply for Medicaid to compare patient health according to the receipt of public insurance coverage [24]. Difference-in-differences analyses compare time trends between a treatment group and nonrandom controls to identify causal relationships. This study design can address many forms of bias and has been used, for instance, to examine the effect of insurance expansion on the use of urologic surgery [25]. In kidney cancer research, a recent study using propensity adjustment and a unique cohort of patients with solitary kidneys, which removes the influence of the contralateral kidney on renal function, has proven crucial for understanding the role of renal parenchyma preservation and ischemia time in outcomes following partial nephrectomy [22].

With no other randomized trials on the horizon, we used a different methodology—instrumental variable analysis—to investigate the potential effect of partial vs. radical nephrectomy on survival in an older but more modern population of patients with clinical category T1a kidney cancer [26]. An instrumental variable analysis is a quasi-experimental, econometric method, which leverages naturally occurring variation to generate pseudorandomization [27]. More often used in the fields of health economics and health services research, this method has been used previously in clinical studies examining the effectiveness of surgery in patients with prostate and bladder cancer [28,29]. To be valid, this method requires the identification of a suitable instrument that meets 2 main conditions: (1) the variable induces substantial variation in treatment and (2) does not relate to the outcome except through its association with the treatment. When these criteria are satisfied, the instrument can be used to balance both measured and unmeasured covariates, allowing for unbiased estimation of the treatment effect in patients whose treatment varied with the instrument.

For our study, we used differential distance to a partial nephrectomy provider—the distance to the nearest surgeon performing partial nephrectomy minus the distance to the nearest surgeon performing any nephrectomy in a given year—as our instrumental variable. Differential distance was used in the classic instrumental variable study on cardiac catheterization and differs from actual distance to a provider [8,27]. During the analytic process, we considered several additional instruments (e.g., minimum distance to a partial nephrectomy provider and regional partial nephrectomy intensity in the preceding year) but found that differential distance had the strongest relationship with treatment (F-statistic = 97.3). Furthermore, the differential difference instrument did not independently predict survival in the presence of other baseline factors. We also noted improved covariate balance within instrument strata relative to the pooled cohort, indicating that we were achieving the intended effect at least on our measurable covariates.

Having satisfied the prespecified conditions to the extent possible, we proceeded with our analysis, hypothesizing that our findings would be commensurate with the randomized controlled trial. Instead, among Medicare beneficiaries with clinical category T1a kidney tumors, we found a survival benefit for patients treated with partial rather than with radical nephrectomy. This advantage appeared most pronounced in patients younger than 75 years and those with a Charlson comorbidity score ≥ 1, and it remained even when limiting our sample to patients with confirmed renal cell carcinoma, residing in urban areas, and treated in