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Treatment Trends for Stage I Renal Cell Carcinoma

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Abbreviations and Acronyms

CoC = Commission on Cancer

NCDB = National Cancer Data Base

RCC = renal cell carcinoma

SEER = Surveillance, Epidemiology and End Results

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Supplementary tables detailing cohort demographics, treatment trends by tumor size and logistic regression analysis for this article can be obtained at http://tiny.ucsf.edu/rcctrend.

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For another article on a related topic see page 681.

Purpose: Renal cell carcinoma is increasingly diagnosed at stage I, and among stage I cases mean tumor size has been decreasing. Previous reports suggest that nephron sparing surgery is underused for small renal cell carcinomas. We determined updated, population based treatment trends for stage I renal cell carcinoma.

Materials and Methods: The National Cancer Data Base, which captures approximately 70% of all cancer diagnoses in the United States, was queried for renal cell carcinoma in adults diagnosed between 1993 and 2007. Trends in treatment, including no surgery, total nephrectomy, partial nephrectomy and focal ablation, were analyzed among all stage I tumors and small stage I tumors categorized by size. Logistic regression was used to identify predictors of nephron sparing surgery (partial nephrectomy or focal ablation).

Results: During the study period we identified 242,740 renal cell carcinomas, of which 127,691 were stage I. For all stage I tumors partial nephrectomy increased from 6.3% to 32.2% of cases and ablation increased from 1.0% to 6.8%. For tumors less than 2.0, 2.0 to 2.9 and 3.0 to 3.9 cm partial nephrectomy increased from 15.3% to 61.1%, 11.0% to 44.2% and 7.2% to 31.1%, respectively (each $p < 0.001$). Female gender, black race, Hispanic ethnicity, lower income, older age and treatment at community hospitals were associated with lower use of nephron sparing.

Conclusions: While total nephrectomy is still likely overused for small renal cell carcinoma, nephron sparing surgery for stage I renal cell carcinoma has increased substantially in the last 15 years with about 4-fold increases across tumor sizes. These trends appear to be ongoing but sociodemographic disparities exist which must be rectified.

Key Words: kidney; carcinoma, renal cell; nephrectomy; trends; epidemiology

An estimated 58,240 tumors of the kidney and renal pelvis, of which most are RCC, were diagnosed in 2010 and approximately 13,040 deaths were expected.[1] The incidence of RCC has increased dramatically in recent years, attributable in large part but not entirely to increased abdominal imaging.[2,3] We previously reported an increase in the proportion of RCCs diagnosed at American Joint Cancer Commission stage I.[4] Even in the stage I group mean tumor size at diagnosis has decreased progressively with time. By 2004, 43.4% of stage I tumors were less than 3 cm at diagnosis and 12.7% were less than 2 cm.[5]

Stage I renal tumors may be managed by radical nephrectomy, active surveillance or nephron sparing

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approaches, including partial nephrectomy and focal ablative procedures. With growing recognition of the favorable oncological outcomes of nephron sparing, and of the potential adverse long-term renal and mortality outcomes after radical nephrectomy, the recently published guideline of the American Urological Association explicitly encourages nephron sparing for most small masses.[6] Recent analysis of the SEER database showed that nephron sparing increased for small RCCs through 2001, although most were still managed by radical nephrectomy.[7] We describe updated trends using NCDB, a larger, highly representative hospital based tumor registry.

PATIENTS AND METHODS

Data Source

NCDB is a joint project of the CoC of the American College of Surgeons and American Cancer Society, established in 1988 and previously described in detail.[8,9] More than 1,400 hospitals, representing approximately 25% of all hospitals in the United States, submit data to NCDB annually through the CoC Accreditation Program. The database comprises data on more than 26 million patients diagnosed between 1985 and 2008, including patient characteristics, tumor staging and histology, primary treatment, cancer recurrence and survival. Since CoC accredited hospitals tend to be higher volume centers than nonaccredited hospitals, accredited hospitals account for 70% of the cancer cases diagnosed annually in the United States.[10]

The American College of Surgeons has executed a data use agreement with each CoC accredited hospital. Privacy is maintained as specified by the Health Insurance Portability and Accountability Act. Data reported to NCDB are retrospective and include no patient identifying information (http://www.facs.org/cancer/ncdb).

Included in analysis were all RCC cases arising in the kidney in adults that were diagnosed between 1993 and 2007, as identified by ICD-O-3 code C64.9. Cases diagnosed before implementation of the American Joint Committee on Cancer Staging Manual, 6th edition, ie before 2002, were restaged using 6th edition criteria.[11] Pathological stage was defined in surgical cases. If pathological findings were not available, clinical stage was assigned from imaging. Cases missing pathological and clinical stage information were excluded from study.

Statistical Analysis

Stage I tumors were 7 cm or less in maximum dimension with no known extrarenal disease. Trends were assessed based on reported primary treatment codes defining total nephrectomy (NCDB codes 40-50), partial nephrectomy (code 30), focal ablation (codes 10-25) or no surgery (code 00). Nephron sparing surgery included partial nephrectomy or a focal ablation procedure. Trends were assessed for all tumors, all stage I tumors and in stage I by size less than 2, 2 to 2.9, 3 to 3.9 and 4 to 7 cm. The statistical significance of trends was determined by the Cochran-Armitage trend test and linear regression was applied to create trend lines.

Logistic regression was used to identify predictors of nephron sparing surgery. In addition to diagnosis year and tumor size, covariates included patient age at diagnosis, gender, race, income quartile based on the median for the ZIP Code of residence, hospital type where treatment was performed and census division (http://www.census.gov/geo/www/us_regdiv.pdf). Urban vs rural hospital site was not a significant predictor in the model ($p = 0.35$). Since many observations did not have data on this variable, it was not included in the final model. Surgery comparisons by hospital type were assessed starting in diagnosis year 1996, when hospital specific surgery type was first collected. Hospital types analyzed included community, comprehensive community and teaching research hospitals (http://www.facs.org/cancer/coc/categories.html).

In 2003 NCDB added comorbidity data collection based on reported ICD-9 coding.[12] Thus, for patients diagnosed in 2003 to 2007 an additional regression model was used to further adjust for diabetes mellitus (complicated and uncomplicated), hypertension, congestive heart failure, obesity, cerebrovascular disease, mild to moderate chronic renal insufficiency (stages I–III) and severe chronic renal insufficiency/end stage renal disease (stages IV–V). Analysis was done using SPSS®, version 18.

RESULTS

A total of 242,740 RCC cases were identified in NCDB from 1993 to 2007, including 127,691 stage I cases and 123,261 with a known surgery type. Mean patient age at diagnosis was 60.8 years (95% CI 60.1–60.9). Downward size migration continued since the prior report of cases through 2004.[5] In 2005 to 2007 size was less than 2, 2.0 to 2.9, 3.0 to 3.9 and 4.0 to 7.0 cm in 13.5%, 23.6%, 22.7% and 40.1% of tumors, respectively. Figure 1 shows overall management trends. The number of stage I cases recorded annually in the database increased with time from 4,274 in 1993 to 14,176 in 2007. The use of total nephrectomy decreased from 88.3% of stage I cases in 1993 to 57.7% in 2007 while partial nephrectomy and focal ablation increased from 6.3% and 1.0% to 32.2% and 6.8%, respectively. The use of surveillance varied from 2.9% to 5.1% with no consistent trend.

We determined surgical management by tumor size. The use of radical nephrectomy decreased from 87.1%, 82.6% and 78.7% for tumors 3.0 to 3.9, 2.0 to 2.9 and less than 2 cm to 57.7%, 40.1% and 24.4%, respectively, from 1993 to 2007 with corresponding increases in partial nephrectomy and ablation, and little change in surveillance. Figure 2 shows substantial, ongoing, almost linear trends in nephron sparing use for small renal lesions in each tumor size subgroup. While the steepest trends were noted for smaller tumors, all trends were statistically significant with a 0.9% to 4.4% annual increase in nephron sparing ($p < 0.001$).

When controlling for other variables, patients diagnosed in 2004 to 2007 were 3.9-fold more likely to undergo nephron sparing than those diagnosed in 1996 to 1999. Female gender, black race, lower in-

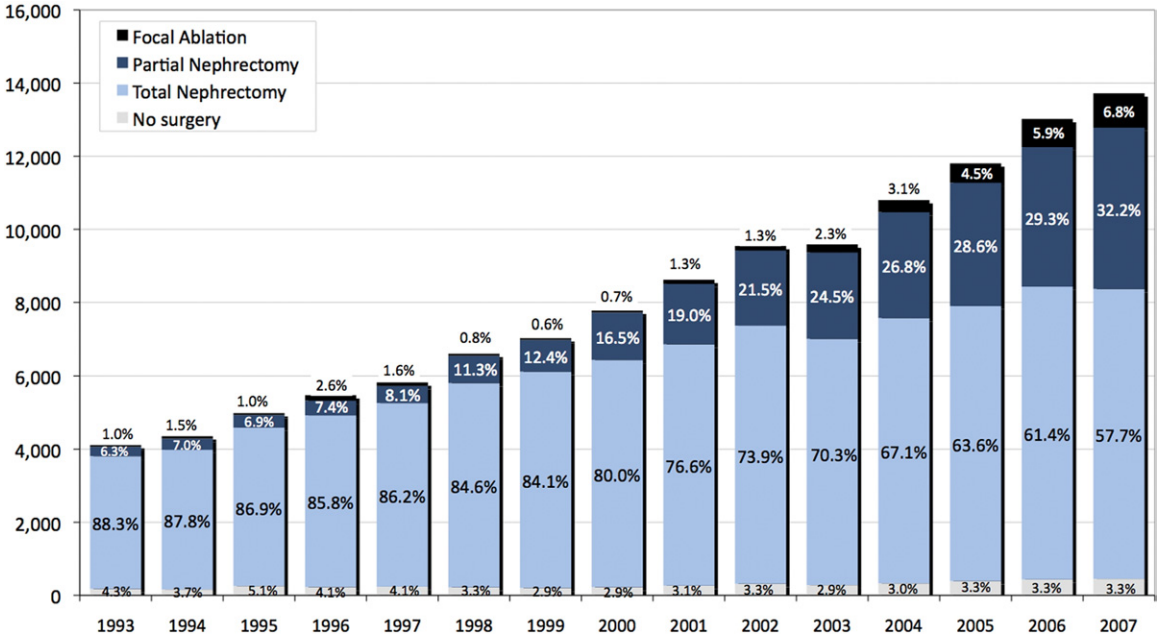

Figure 1. Overall trends in management for stage I renal tumors. Bars indicate total number of cases accessioned in NCDB. Values on bars indicate case distribution across 4 treatment modalities.

come and older age were associated with lower odds of nephron sparing. When controlling for other variables, there was also variation by region with the lowest odds of nephron sparing in east south central states (Alabama, Kentucky, Mississippi and Tennessee) and the highest in west north central states (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota and South Dakota). At all times and for all tumor sizes patients treated at teaching/research hospitals were more likely to undergo

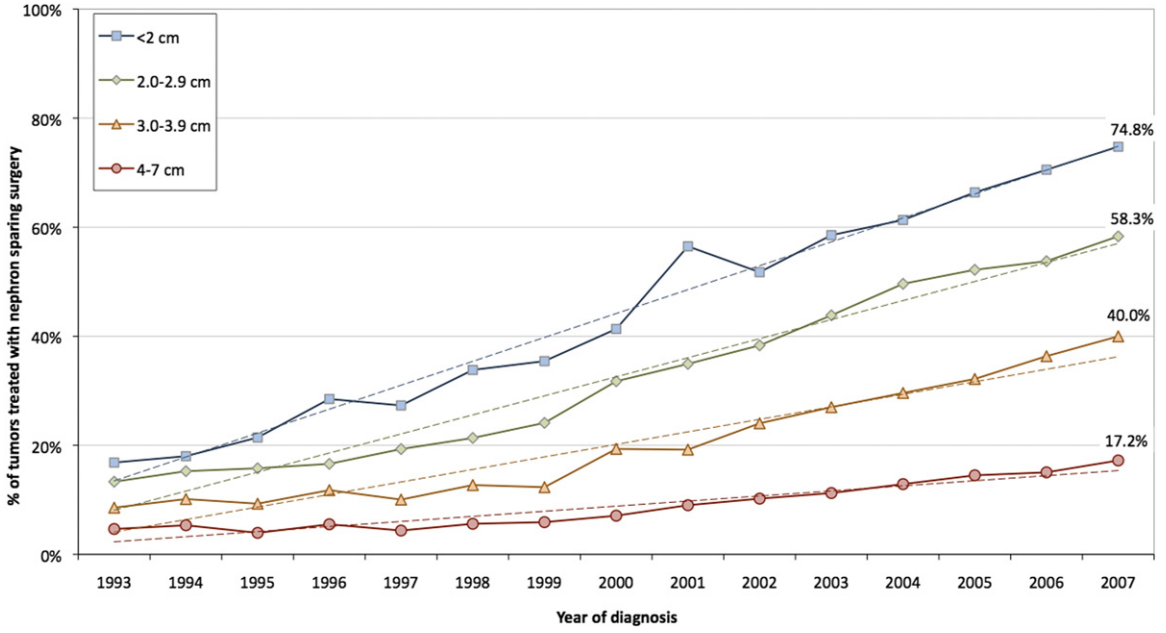

Figure 2. Trends in nephron sparing surgery for stage I renal tumors. For each year percent of tumors managed by nephron sparing with partial nephrectomy or focal ablation is shown relative to total number of cases. Data are plotted for each tumor size subcategory and regression lines were drawn based on univariate linear regression. Mean annual increase nephron sparing was 4.4%, 3.5%, 2.3% and 0.9% for tumors less than 2, 2 to 2.9, 3 to 3.9 and 4 to 7 cm, respectively.

nephron sparing surgery than those treated at community hospitals. For example, 47.8%, 53.5% and 66.8% of tumors less than 3 cm diagnosed between 2004 and 2007 at community, comprehensive community and teaching/research hospitals, respectively, were treated with nephron sparing. However, in recent years the use of nephron sparing for smaller masses has increased rapidly across hospital types (fig. 3).

Multivariate regression incorporating comorbidity in patients diagnosed from 2003 to 2007 included 49,391 patients. Hypertension was not associated with nephron sparing (OR 1.04, 95% CI 0.99–1.09). Uncomplicated diabetes predicted nephron sparing (OR 1.26, 95% CI 1.19–1.34) while complicated diabetes and cerebrovascular disease showed nonsignificant trends toward nephron sparing (OR 1.19, 95% CI 0.98–1.44 and 1.29, 95% CI 0.99–1.69, respectively). Congestive heart failure and obesity were not predictive of nephron sparing. Patients with stage I–III chronic renal insufficiency were likely to undergo nephron sparing (OR 1.60, 95% CI 1.08–2.38) while those with stage IV–V renal insufficiency/end stage renal disease were relatively unlikely to undergo nephron sparing (OR 0.30, 95% CI 0.25–0.35). No other clinical or sociodemographic parameter estimates in the model were substantially altered by adding the comorbidity variables.

DISCUSSION

Increased early detection of low stage renal tumors has decreased the proportion of tumors diagnosed at advanced stages but not the age adjusted incidence rate of advanced disease.[3] While 5-year survival for kidney cancer has increased with time,[13] this trend primarily reflects imaging driven stage migration. At the population level the mortality rate of kidney cancer decreased only 3.9% in men and 7.8% in women from 1990 to 2005 compared to, for example 36.1% for prostate cancer and 26.6% for breast cancer.[14] Another analysis based on SEER data showed increases in the RCC mortality rate with time through 2001. These increases were noted for all tumor sizes but were most prominent for those greater than 7 cm.[2]

These epidemiological observations raise questions regarding the oncological impact of intervention for low stage, incidentally detected renal lesions. In fact, concerns regarding the over diagnosis of and overtreatment for these tumors are analogous to those increasingly raised with respect to low risk prostate cancer.[15] While the decrease in quality of life due to uncomplicated interventions for renal tumors may be low, the impact of even relative renal insufficiency on overall survival is increasingly apparent. A recent large series of stage T1a renal tumors showed an almost 4-fold increase in renal insufficiency after radical rather than partial nephrectomy.[16] Another showed a doubled risk of overall mortality in patients younger than 65 years treated with radical rather than partial nephrectomy even after adjusting for preoperative renal function and other potential confounding variables.[17] Most recently a large, single center series confirmed this finding in patients of all ages.[18]

With gradual acceptance of the oncological safety of nephron sparing surgery[19] and more recently of the importance of renal preservation, nephron sparing use has been increasing. For example, an analysis of SEER showed that nephron sparing interventions increased from 5% in 1988 to 18% in 2001 with increases for lesions less than 2 and 2 to 4 cm from 14% to 42% and from 5% to 20%, respectively.[7]

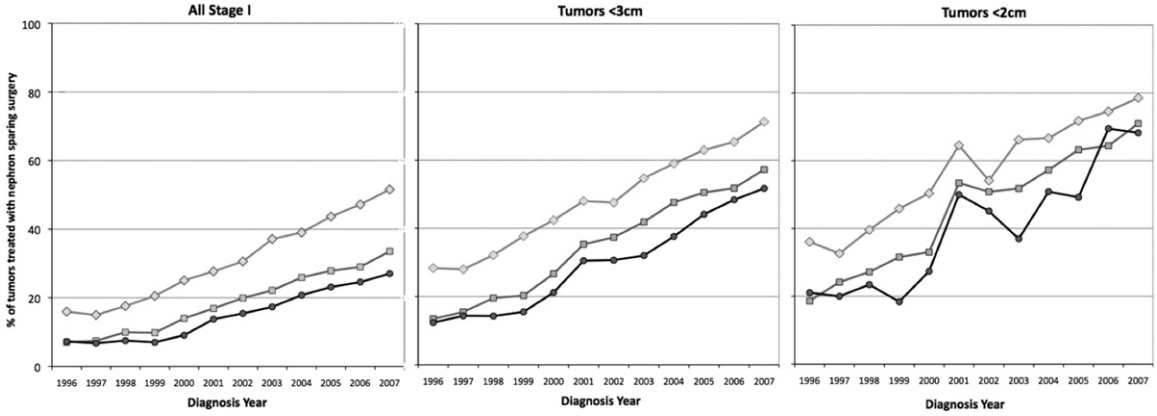

Figure 3. Trends in nephron sparing surgery for stage I renal tumors by hospital type, including teaching research (diamonds), comprehensive community (squares) and community (circles). For each year percent of tumors managed by nephron sparing with partial nephrectomy or focal ablation is shown relative to total number of cases. Data are presented for all stage I tumors, and tumors less than 3 and less than 2 cm.

A more contemporary SEER study documented an increase in the partial nephrectomy rate as of 2006 of up to 45% for 2 to 4 cm lesions.[20] We find strong evidence that these trends are ongoing with the highest rates of nephron sparing yet reported for small renal masses. In the American Urological Association guideline partial nephrectomy is now considered the explicitly preferred standard of care for stage T1a tumors and an alternative standard of care even for stage T1b tumors. Thermal ablation and active surveillance are alternatives in select cases and radical nephrectomy for T1a tumors should be reserved for those that are deemed not technically amenable to partial nephrectomy.[6]

The feasibility of nephron sparing surgery varies according to surgeon experience and expertise. The diffusion of partial nephrectomy has been affected and perhaps impaired by the progressive adoption of laparoscopy by urologists.[7,21] A SEER-Medicare analysis showed that after adjusting for tumor and patient characteristics, surgeon practice style accounted for 18% and 37% of the observed variance in the use of partial nephrectomy and of laparoscopic renal surgery, respectively.[21] In expert hands minimally invasive nephron sparing surgery is an increasingly viable option even for T1b and larger tumors, yielding oncological outcomes similar to and renal functional outcomes superior to those of radical nephrectomy.[22] A recently proposed classification system to standardize the difficulty of the surgical approach to a given tumor offers promise, if broadly adopted, to risk adjust analyses across different series and contexts.[23]

Most renal masses less than 3 cm and most stage I tumors of any size treated at teaching hospitals are now treated with nephron sparing. The rate of partial nephrectomy increased more than 4-fold between 1993 to 1995 and 2005 to 2007, and the acceleration in the uptake of focal ablation for small masses has been even more rapid. Nonetheless, a total nephrectomy rate of 60.8% in 2005 to 2007 for all stage I masses and 28.1% even for tumors less than 2 cm is likely still too high.

There was little evidence in the NDCB data of any trend toward increased surveillance for small masses. Even of lesions less than 2 cm managed in 2005 to 2007 only 3.5% were not treated surgically. A meta-analysis of 9 surveillance series revealed a mean growth rate of 0.28 cm annually during a median 32-month followup and in cases confirmed to be RCC the growth rate was 0.4 cm annually. While these data tend to support a larger role for surveillance, a subset of tumors grow more quickly. Moreover, the growth rate cannot be predicted from size at diagnosis or other radiographic characteristics and rare cases of metastatic progression have been reported.[24]

Another recent meta-analysis showed no significant difference in the metastasis rate among tumors managed by resection, ablation or surveillance, although followup in most underlying series remains relatively short.[25] A competing risk analysis in 1 large series demonstrated that in patients older than 75 years active intervention for clinically localized RCCs up to 7 cm had no impact on survival compared to surveillance.[26] Surveillance is endorsed by the guideline as a recommendation for patients with small masses and significant comorbidity, and as an option for those in better health.[6]

We found differences in the use of nephron sparing across sociodemographic groups. After adjustment female gender, black race, Hispanic ethnicity and lower income were independently associated with lower odds of nephron sparing. Variation was also observed across geographic regions. A recent SEER analysis focusing on tumors 4 cm or less showed similar age and gender biases for partial nephrectomy use as well as a trend toward lower use in black patients.[20] These findings cannot be immediately explained but certainly suggest a pervasive treatment disparity across sociodemographic groups. Even in a large, recently reported academic series the adjusted OR of partial nephrectomy in women vs men was 0.72 (95% CI 0.54–0.96) and even with the greater clinical detail available in this cohort there was no clear explanation for this difference.[24] Overall, patients with risk factors for cardiovascular disease, particularly diabetes, were appropriately more likely to undergo nephron sparing, as were those with existing renal insufficiency. Conversely those with severe renal insufficiency or established end stage renal failure were more likely to undergo total nephrectomy.

Caveats to this analysis should be noted. NCDB captures only confirmed cases of kidney cancer reported to tumor registries. Thus, benign renal lesions are not included, nor are most cancers that are ablated or observed without biopsy. The likelihood of benignity varies inversely with tumor size since about 25% of lesions 2 to 3 cm and 30% of those less than 2 cm are benign.[25] Therefore, to the extent that smaller masses are more likely to be ablated rather than resected our findings may underestimate the proportion of enhancing renal masses, as opposed to confirmed RCC, managed by nephron sparing in general and surveillance or focal ablation in particular. Notably the practice guideline strongly encourages biopsy for masses treated with ablation.[6]

While NCDB includes a large proportion of patients with cancer treated in the United States, patients are not a random sample of the whole population. Those treated at hospitals not participating in the CoC accreditation program are not included. Thus, approximately 30% of patients with cancer

are treated at a large number of low volume, nonaccredited centers, where practice patterns might be substantially different from those at the accredited academic and community based centers. For example, nonaccredited hospitals are smaller and more likely to be located in rural areas, less surgery is done and they are less likely to offer oncology services.[10] In contrast, the current analysis complements and builds on prior national studies in important ways. For example, NCDB offers the advantages of a broader geographic representation of the American population than SEER and unlike SEER-Medicare it is not limited to patients older than 65 years.

NCDB does not include information on surgical approach (open vs laparoscopic vs robotic assisted). Since 2004, when the first robotic assisted laparoscopic partial nephrectomy was reported, interest in this procedure has been growing rapidly.[26] It is too soon to determine the impact of the subsequent diffusion of this technology and expertise on overall management trends but it might be expected that by decreasing technical barriers to laparoscopic partial nephrectomy robotic assistance may accelerate the observed trends. Updating this analysis in coming years will be important as additional data and experience accrue.

CONCLUSIONS

While total nephrectomy is still likely overused for small renal masses, the use of nephron sparing approaches for stage I RCC has increased approximately 4-fold in the last 15 years. Nephron sparing is done most consistently at academic centers, although the gap appears to be narrowing for the smallest tumors. Comorbid illness appropriately modifies the likelihood of nephron sparing in most cases. However, the significant disparity in nephron sparing utilization rates by gender, race and income, even with adjustment for tumor size, surgery year, comorbidity and hospital type, is troubling, and merits further research and efforts at remediation.

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