BRIEF COMMUNICATIONS

Rising Incidence of Small Renal Masses: A Need to Reassess Treatment Effect

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The incidence of kidney cancer has been rising over the last two decades, especially in cases where the disease is localized. Although rates of renal surgery parallel this trend, mortality rates have continued to rise. To investigate the basis of this "treatment disconnect" (i.e., increased rates of treatment accompanied by increased mortality rates), we analyzed patient data from nine registries of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. We assembled a cohort of 34 503 kidney cancer patients and derived incidence, treatment, and mortality trends for kidney cancer, overall and as a function of tumor size. From 1983 to 2002, the overall age-adjusted incidence rate for kidney cancer rose from 7.1 to 10.8 cases per 100 000 US population; tumors ≤4 cm in size accounted for most of the increase. Adjusted rates of renal surgery increased concurrently, most notably for tumors ≤4 cm (0.9–3.6 surgeries per 100 000 US population). However, among kidney cancer patients, all-cause mortality per 100 000 US population increased from 1.5 deaths in 1983 to 6.5 deaths in 2002, with the greatest absolute increase noted for patients with lesions >7 cm. Our results demonstrate that the rising incidence of kidney cancer is largely attributable to an increase in small renal masses that are presumably curable. The fact that increased detection and treatment of small tumors is not reducing mortality argues for a reassessment of the current treatment paradigm. [J Natl Cancer Inst 2006;98:1331–4]

Over the last 20 years, the annual incidence of renal cell carcinoma has been rising, with the greatest increase observed for cases with localized tumors *(1–4)*. For more than four decades, the treatment paradigm for solid renal masses has favored their expedient removal upon detection *(5)*. Consequently, an increase in the rate of extirpative surgery has paralleled the rising incidence of renal cell carcinoma *(6)*. The current treatment paradigm is based on the assumption that early intervention (i.e., treatment of presumably early, low-stage disease) will achieve better survival outcomes *(7,8)*. If it is correct, then its application should lead to lower kidney cancer mortality rates among patients with early, low-stage renal cell carcinoma. However, this assumption is not supported by population-based mortality data *(1,3)*. This apparent disconnect—between increasing treatment and increasing mortality—suggests a need for careful assessment of the benefits of surgery for small renal masses. Therefore, we examined incidence and practice patterns for kidney cancer as a function of tumor size.

We used data from the nine original Surveillance, Epidemiology, and End Results (SEER) registries (San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta, San Jose-Monterey, Los Angeles, Alaska) of the National Cancer Institute to identify incident cases of kidney cancer (n = 40 813) based on *International Classification of Diseases for Oncology, Second Edition (9)* site code C64.9; histology codes 8032, 8041, 8240, 8260, 8270, 8290, 8310, 8312, 8317, 8318, 8319, 8320, 8960, 8963, and 8966; and behavior codes 2 and 3 (for adenocarcinoma in situ and adenocarcinoma, NOS, respectively) occurring between 1983 and 2002.

Over the study period, 34 503 kidney cancer cases with data regarding pretreatment tumor size were identified, and these constituted the study cohort. Patients (n = 6310) without tumor size data were excluded. Demographic and cancer-specific data, including age at diagnosis, race, gender, tumor laterality, organ-confined status, and tumor histology, were extracted. With the exception of patient age treated as a continuous variable, all of these factors were treated as categorical variables. Cases of kidney cancer were sorted into four tumor size categories (<2, 2–4, >4–7, and >7 cm in size).

The patients excluded because of missing tumor size data were equally distributed across the nine SEER sites (data not shown). Compared with the patients for whom tumor size data were available, excluded patients were more likely to be older (Table 1) (mean age = 65.6 years versus 61.9 years, mean difference = 3.7, 95% confidence interval [CI] = 3.3 to 4.1, $P<.001$), more likely to have non–organ-confined disease at diagnosis (for those with tumor size data, 64% had organ-confined disease versus 27% of those without tumor size data, mean difference = 37%, 95% CI = 35% to 39%, $P<.001$), and more likely to forego surgical treatment (for those with tumor size data, 84% underwent surgical treatment versus 31% of those without tumor size data, mean difference = 53%, 95% CI = 52% to 54%, $P<.001$). Collectively, the demographic and tumor-specific data suggested that patients with unknown tumor size were most similar to those patients with tumors >7 cm. Since our analytic focus was on patients with small renal masses (≤4 cm), multiple imputation—a statistical method of "filling in" several values for each missing data point to incorporate the uncertainty due to missing data—was not performed.

Incidence rates for kidney cancer were calculated by determining the number of cases diagnosed each year, dividing by the corresponding mid-year population estimates provided by SEER, and multiplying by 100 000. Rates were age adjusted to the 2000 US population using direct adjustment methods. To determine the annual incidence rates for surgical intervention, patients were categorized as having received definitive surgical treatment (including partial nephrectomy, total nephrectomy, and ablative therapies), palliative radiation, or no intervention. Age-adjusted annual

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Table 1. Demographic and pathologic data* for SEER renal cell carcinoma patients diagnosed between 1983 and 2002 according to tumor size

Characteristic	Tumor size†				
	<2 cm (n = 1637)	2–4 cm (n = 9676)	>4–7 cm (n = 11 372)	>7 cm (n = 11 818)	Missing (n = 6310)
Patient characteristics					
Mean age ± standard deviation (years)‡	60.7 ± 15.0	63.5 ± 13.7	63.2 ± 14.1	59.4 ± 18.3	65.6 ± 16.3
% Female§	38.3	38.1	37.6	36.3	37.8
Race (%)‡					
White	82.0	83.7	86.2	85.6	85.0
Black	13.4	11.4	8.8	9.0	10.7
Other	4.6	4.9	5.0	5.4	4.3
Tumor characteristics					
% Right§	52.9	53.5	51.4	48.5	47.9
% Organ confined‡	88.1	85.1	66.3	40.1	27.4
Tumor histology (%)‡					
Clear cell	90.6	92.0	92.5	88.3	89.6
Papillary	3.3	2.4	1.5	1.0	0.9
Chromophobe	0.2	0.2	0.1	0.1	0.0
Oncocytoma	0.1	0.3	0.1	0.1	0.1
Other	5.8	5.1	5.8	10.5	9.4
Fuhrman grade (%)‡					
1	36.2	32.4	22.9	14.3	20.1
2	47.3	51.6	50.1	42.6	34.3
3	12.8	14.0	22.0	32.8	35.9
4	3.7	2.0	5.0	10.3	9.7

*From nine Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta.

†For those cases with available tumor size data, chi-square tests were used to compare all categorical variables; Mantel–Haenszel chi-square tests were performed for all ordinal variables; generalized linear modeling was performed for continuous variables.

‡For $P<.001$.

§For $P<.05$.

rates of renal surgery and mortality rates (overall and cancer-specific) were calculated using the same methodology as for kidney cancer incidence rates.

All statistical tests were two-tailed and performed at a significance level of .05 using the SAS system (version 9.1, SAS Institute, Cary, NC). Institutional Review Board approval was waived for this study.

The demographic and clinicopathologic characteristics of our sample are shown in Table 1. We observed that new diagnoses were more common in men than in women across all tumor size strata. Based on bivariate analysis, those patients with tumors >7 cm in size were more likely to be diagnosed at a younger age than those with tumors ≤7 cm ($P<.001$). We observed that a higher proportion of blacks had small (≤4 cm in size) versus large (>4 cm) masses ($P<.001$). The results of our chi-square analysis revealed that the percentage of patients with localized disease decreased with increasing tumor size ($P<.001$).

We found that from 1983 to 2002 the overall incidence of kidney cancer rose from 7.1 (95% CI = 6.7 to 7.5) to 10.8 (95% CI = 10.4 to 11.2) cases per 100 000 US population, an increase of 52% (data not shown). We then calculated the annual incidence of kidney cancer and surgery for each of the four categories of tumor size over the same period. Incidence of kidney cancer in which tumors were 2–4 cm in size rose from 1.0 (95% CI = 0.8 to 1.1) cases per 100 000 in 1983 to 3.3 (95% CI = 3.1 to 3.5) cases per 100 000 in 2002 (Fig. 1, A), representing the largest increase in terms of absolute numbers. During this time, incidence of kidney cancer (cases per 100 000 US population) increased from 0.2 (95% CI = 0.1 to 0.3) to 0.8 (95% CI = 0.7 to 0.9) for tumors <2 cm in size, from 2.0 (95% CI = 1.8 to 2.2) to 3.0 (95% CI = 2.8 to 3.2) for tumors >4–7 cm in size, and from 2.3 (95% CI = 2.1 to 2.5) to 2.9 (95% CI = 2.7 to 3.1) for tumors >7 cm in size. Cases in which lesions were <2 cm and 2–4 cm rose the most in relative terms (285% and 244% from 1983 to 2002, respectively).

For each tumor size category, the annual incidence of renal surgery was nearly identical to the annual incidence of kidney cancer, throughout the period from 1983 to 2002 (Fig. 1, B). Thus, trends in renal surgery mirrored trends in kidney cancer incidence.

From 1983 to 2002, kidney cancer–specific and overall mortality rates rose from 1.2 (95% CI = 1.1 to 1.3) to 3.2 (95% CI = 3.0 to 3.4) deaths per 100 000 US population and from 1.5 (95% CI = 1.3 to 1.7) to 6.5 (95% CI = 6.2 to 6.8) deaths per 100 000 US population, representing a 155% and 323% increase, respectively. Over the study interval, cancer-specific mortality rates rose for each of the four categories of tumor size (Fig. 2, A): from 0.01 (95% CI = 0.00 to 0.03) to 0.03 (95% CI = 0.01 to 0.05) for tumors <2 cm, from 0.03 (95% CI = 0.01 to 0.05) to 0.3 (95% CI = 0.2 to 0.3) for tumors 2–4 cm, from 0.2 (95% CI = 0.1 to 0.2) to 0.7 (95% CI = 0.6 to 0.8) for tumors >4–7 cm, and from 0.3 (95% CI = 0.2 to 0.3) to 1.4 (95% CI = 1.3 to 1.5) for tumors >7 cm. During this time, overall mortality rates also increased across all tumor size strata (Fig. 2, B): 0.07 (95% CI = 0.03 to 0.1) to 0.2 (95% CI = 0.2 to 0.3) for tumors <2 cm, 0.2 (95% CI = 0.1 to 0.2) to 1.5 (95% CI = 1.3 to 1.6) for tumors 2–4 cm, 0.3 (95% CI = 0.2 to 0.3) to 1.7 (95% CI = 1.6 to 1.9) for tumors >4–7 cm, and 0.4 (95% CI = 0.3 to 0.4) to 2.2 (95% CI = 2.0 to 2.3) for tumors >7 cm. Thus, despite more frequent surgical treatment for kidney cancers characterized by small tumors, mortality among patients with renal cell carcinoma has continued to increase.

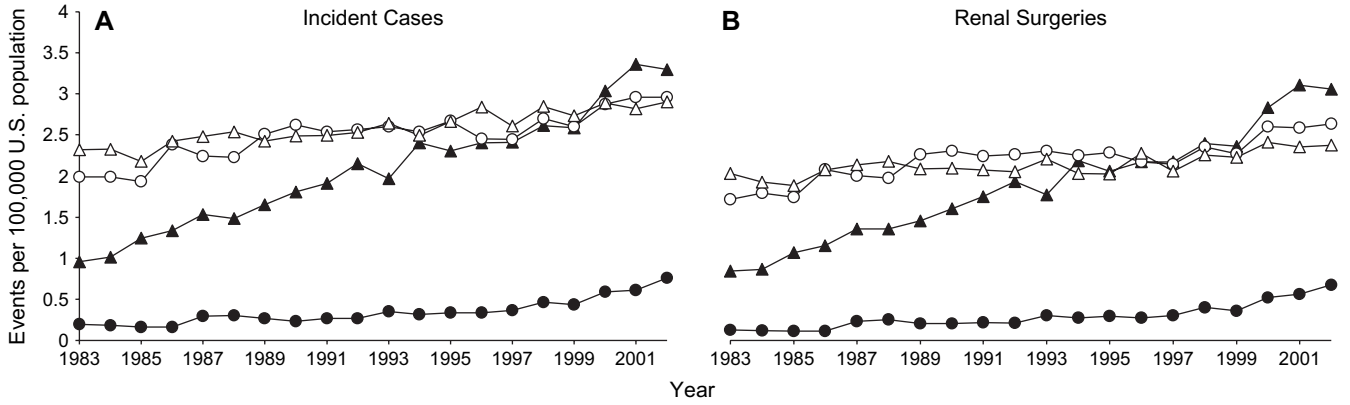

Fig. 1. Age-adjusted (2000 US) annual kidney cancer incidence (**A**) and annual rates of renal surgery (**B**), stratified by tumor size. Rates are expressed as the number of events per 100 000 US population. ● = <2 cm, ▲ = 2–4 cm, ○ = >4–7 cm, and Δ = >7 cm. Data used to calculate incidence of kidney cancer and rates of renal surgery were obtained from nine Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta.

This study demonstrates that the rise in incidence of renal cell carcinoma *(1–4)* is largely a result of the increasing detection of small (≤4 cm) tumors. Given the current treatment paradigm for localized kidney cancer, it is not surprising that the observed incidence trend is paralleled by a corresponding rise in surgical intervention. However, despite increased detection and treatment of small masses, mortality rates for kidney cancer have continued to rise. Collectively, these trends raise questions about the effectiveness of the current treatment paradigm for kidney cancer.

The incidence and prevalence of a disease are intimately related to diagnostic capabilities. When a technological advance improves the ability to detect a disease, the incidence and prevalence of the disease will rise *(10)*. The effect of cross-sectional imaging on kidney cancer incidence is a case in point.

Advanced cross-sectional imaging allows for tumor detection well before any clinical signs or symptoms become apparent, such that more tumors have moved from the undetectable to the detectable range. The results reported here suggest that with the discovery of more tumors in this preclinical phase, incident cases are increasingly ones in which tumors are small. This stage migration has increased the absolute number of curable lesions that are detected. Do all these tumors have a universal capacity to grow and metastasize? Do they need to be treated promptly? The prevailing opinion among surgeons to both these questions is yes. As evidenced by our current work, treatment of these small, curable tumors has increased. But while population-based observational data have demonstrated a resultant rise in the relative 5-year survival rates over the last three decades *(11)*, the mortality rates for kidney cancer have continued to increase.

How can these seemingly contradictory findings be reconciled? In part, lead-time and length biases account for this inconsistency. Lead-time bias results from those comparisons made on a disease's response to an intervention without any adjustment for the timing of the disease's diagnosis. Length bias refers to those comparisons that are unadjusted for the rate of progression of the disease. Both these biases can produce an apparent improvement in patient outcomes, even if the intervention confers little or no mortality benefit *(10)*.

Second, with more than 60% of kidney cancers discovered unexpectedly in patients who undergo diagnostic evaluation for an unrelated condition *(12)*, more and more small detectable (presumably curable) lesions are being treated; however, the absolute number of

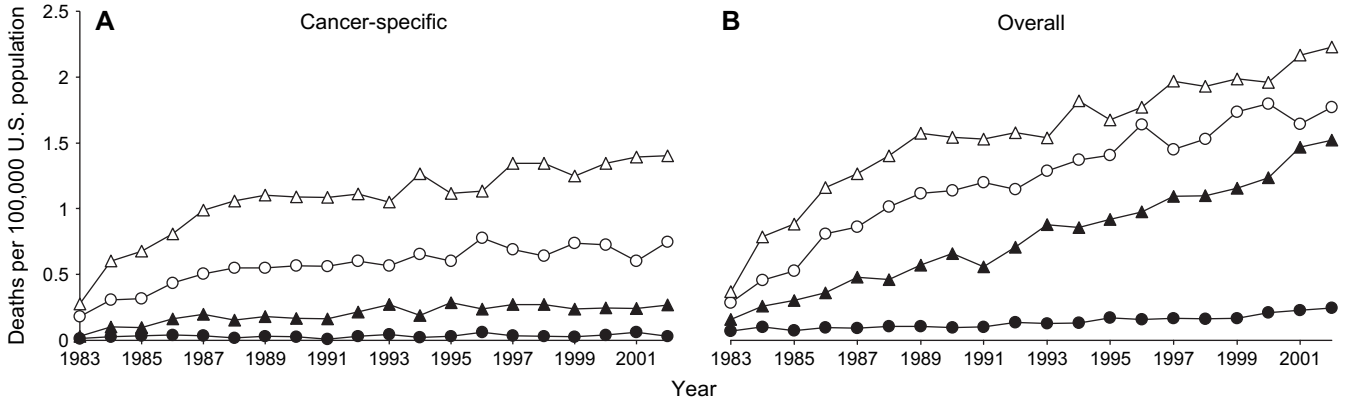

Fig. 2. Age-adjusted (2000 US) kidney cancer–specific (**A**) and overall (**B**) annual mortality rates stratified by tumor size. Rates are expressed as the number of deaths per 100 000 US population. ● = <2 cm, ▲ = 2–4 cm, ○ = >4–7 cm, and Δ = >7 cm. Data used for kidney cancer–specific mortality and overall mortality were obtained from nine Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta.

patients with detectable lethal lesions has not diminished. And it is these larger, lethal masses that mainly mediate mortality (Fig. 2, A and B). Because surgery cures only a fraction of these cancers, mortality is unaffected. Taken together, these data would suggest that at least a proportion of these small detectable lesions represent an indolent form of kidney cancer that may not merit surgical intervention.

These data do not encourage an abrupt departure from the current treatment paradigm for kidney cancer; rather, they prompt reflection on our clinical practice and suggest the need for investigation to address the observed "treatment disconnect" that we are treating more and more small renal masses but are not impacting mortality. The findings from our study should be tempered by considering the following limitations. SEER does not collect data on patient comorbidity, which affects treatment decisions and survival. Additionally, 15% of the identified cases of kidney cancer lacked tumor size information. These patients were characterized with the data available. In general, those tumors for which size information was missing occurred more frequently in older patients with advanced disease, who were less likely to undergo definitive surgical therapy. In aggregate, this group of patients resembled patients with larger cancers rather than smaller ones. As such, the exclusion of these missing data may have resulted in an underestimation of the incidence and mortality rates for renal lesions >7 cm in size.

In summary, our study demonstrates that the rising incidence of kidney cancer manifested in the past two decades is largely attributable to the increase in small renal masses. This increase in incidence of the small renal mass has been paralleled by an increase in surgical treatment. However, these trends have not translated into improvements in mortality rates for kidney cancer, suggesting that these smaller cancers, or at least a proportion of them, represent an indolent form of renal cell carcinoma that may not merit surgical removal. 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 with small renal tumors.

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Notes

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