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Decreasing Size at Diagnosis of Stage 1 Renal Cell Carcinoma: Analysis From the National Cancer Data Base, 1993 to 2004

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Purpose: The proportion of renal cell carcinoma cases diagnosed at stage I is known to be increasing significantly. We characterized stage I tumors further in terms of tumor size at diagnosis using a large national cancer registry.

Materials and Methods: The National Cancer Data Base captures approximately 75% of all newly diagnosed cancer cases in the United States. The database was queried for all adults who were diagnosed between 1993 and 2004 with stage I renal cell carcinoma. Trends were assessed in mean size with time as well as in the proportion of stage I tumors diagnosed at less than 2.0, less than 2.5 and less than 3.0 cm.

Results: There were 104,150 patients in the National Cancer Data Base diagnosed with stage I renal cell carcinoma during the study period. A total of 10,279 stage I tumors (9.9%) were less than 2.0 cm, 26,621 (25.6%) were 2.5 cm or less and 39,879 (38.3%) were 3.0 cm or less. Analysis of stage I renal cell carcinoma diagnoses with time demonstrated a statistically significant increase in the proportion of renal masses 3.0 cm or less between 1993 and 2004 (32.5% vs 43.4%). Of tumors 3.0 cm or less the proportion smaller than 2.0 cm increased significantly during the study period from 24.1% in 1993 to 29.4% in 2004. Mean tumor size decreased from 4.1 to 3.6 cm between 1993 and 2004 ($p < 0.001$).

Conclusions: Tumor size at diagnosis is decreasing with time in patients with stage I renal cell carcinoma. These data likely underestimate the proportion of all enhancing renal masses diagnosed at a small size. Patients with small masses may be appropriate candidates for nephron sparing surgery, energy based ablative therapy or active surveillance. Better technologies are needed to determine the diagnosis and prognosis of small enhancing renal masses.

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

An estimated 51,190 men and women in the United States were diagnosed with cancer of the kidney in 2007 with 12,890 expected deaths.¹ In terms of incidence and mortality most of these cases were due to RCC. The incidence and mortality of RCC across disease stages are known to be increasing with the greatest escalation in incidence primarily attributable to the increasing diagnosis of localized tumors.^{2,3} We have previously reported a significant increase in the proportion of RCCs diagnosed at AJCC stage I, defined as a tumor 7 cm or less that is confined to the kidney, from 42.9% of all RCCs in 1993 to 56.3% in 2003 ($p < 0.05$).⁴ However, within stage I management strategies vary significantly. Smaller tumors are more likely to be treated with nephron sparing surgery or energy based ablation and more likely to be potential candidates for surveillance in select cases. To our knowledge trends in stage I tumor size at diagnosis have not previously been described

in detail. Therefore, we analyzed these patterns using a large, population based national tumor registry.

METHODS

The NCDB, which is a joint project of the Commission on Cancer of the American College of Surgeons and American Cancer Society, is a cancer management and outcomes database for health care organizations that was inaugurated in 1989. Reporting to NCDB is a requisite for Commission on Cancer approved cancer program designation. Thus, 1,400 facility based cancer registries report data to the NCDB, which captures an estimated 75% of all new cancer diagnoses in the United States annually. Data reported include patient characteristics, tumor staging and histology, primary treatment, disease recurrence and survival information. Data quality is closely monitored by the NCDB quality integration committee and confidentiality is protected in compliance with Health Insurance Portability and Accountability Act standards. The NCDB currently includes approximately 20 million cases of reported cancer diagnosed between 1985 and 2004, and it has been described in further detail previously (Appendix 1).⁵

We queried the NCDB for adults (18 years or older) diagnosed between 1993 and 2004 who presented with renal cell tumors arising in the kidney (ICD-O-3 code C64.9) with

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Study complied with 1996 Health Insurance Portability and Accountability Act privacy requirements.

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a behavior code of 3, indicating malignant disease. Appendix 2 lists specific included ICD-O-3 histology codes. Clinical and pathological staging information was available in the database. Tumors were staged according to the AJCC, 6th edition,⁶ using AJCC pathological stage group and supplemented by AJCC clinical stage group when pathological stage was not recorded. Cases diagnosed before the implementation of the 6th edition were restaged using 6th edition criteria. Pathological stage I lesions were defined for surgical patients who had complete pathological information available for review. Appendix 2 lists included surgery codes. Trends were assessed using best stage, ie pathological stage when available, and clinical stage when pathological stage was not available, and including only cases with pathological stage available. Cases missing stage information were excluded.

Trends were evaluated among stage I tumors by evaluating changes in mean size with time, assessing the proportion of stage I tumors less than 3 cm, and further grouping these small stage I lesions into less than 2.0, 2.0 to 2.5 and 2.6 to 3.0 cm. Statistical significance of trends was evaluated with the Cochran-Armitage trend and t tests for mean differences between 1993 and 2004. Analyses were performed with SPSS®, version 14.0 and SAS®, version 9.1 for the Cochran-Armitage trend test.

Data reported to the NCDB are retrospective in nature. No patient or physician identifiers were collected as part of the study. Case identification information (facility identification number and local registry accession number) was collected for administrative purposes only. Analyses were reported only at the aggregate level to assist hospital cancer programs with quality assurance, rather than used to make decisions about individuals and their care. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its approved hospitals. Results reported in this study were in compliance with the privacy requirements of the Health Insurance Portability and Accountability Act of 1996 as re-

ported in the Standards for Privacy of Individually Identifiable Health Information; Final Rule (45 CFR Parts 160 and 164).

RESULTS

A total of 104,150 stage I RCC cases were identified in the NCDB for diagnosis years 1993 to 2004. The number of stage I RCCs in the NCDB increased with time from 5,335 cases in 1993 to 11,650 in 2004 (fig. 1). During this 12-year period there were 10,279 stage I tumors (9.9%) less than 2.0 cm, 26,621 (25.6%) 2.5 cm or less and 39,879 (38.3%) 3.0 cm or less. Figure 2 shows the increase with time in the percent of tumors less than 2.0, 2.0 to 2.5 and 2.5 to 3.0 cm in the broader group of stage I tumors. Overall tumors less than 3.0 cm increased from 32.5% in 1993 to 43.4% in 2004 (test for trend $p < 0.001$). Between 1993 and 2004 mean tumor size in the stage I group decreased from 4.13 to 3.69 cm as assessed by pathological stage (t test $p < 0.001$) and from 4.06 cm to 3.64 cm as assessed by best stage (t test $p < 0.001$, fig. 3).

Of all tumors less than 3.0 cm the percent less than 2.0 cm increased from 24.1 in 1993 to 29.4 in 2004 (test for trend $p < 0.0001$). The percent of 2.0 to 2.5 cm lesions decreased slightly from 41.1 to 39.9 (test for trend $p > 0.05$), while the percent of 2.6 to 3.0 cm tumors decreased from 34.7 to 30.7 (test for trend $p < 0.001$).

DISCUSSION

Given the diagnosis of kidney cancer, expected 5-year survival increased from 51% in 1974 to 1977, to 56% in 1984 to 1986 and to 66% in 1996 to 2002.¹ Much of this improvement in survival is likely attributable to the increasing use of soft tissue imaging for evaluating a wide variety of abdominal and pelvic symptoms with the resulting incidental discovery of a growing number of renal masses. Such incidentally discovered tumors are curable via surgical extirpation more

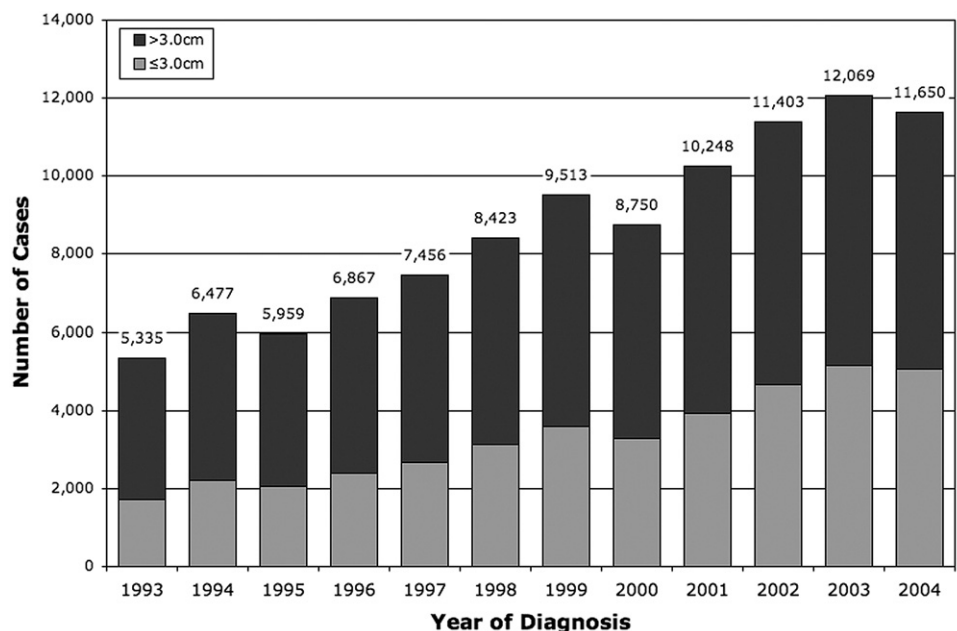


FIG. 1. Number of stage I RCC cases in 1993 to 2004 by diagnosis year according to tumor size 3.0 cm or less vs greater than 3.0 cm

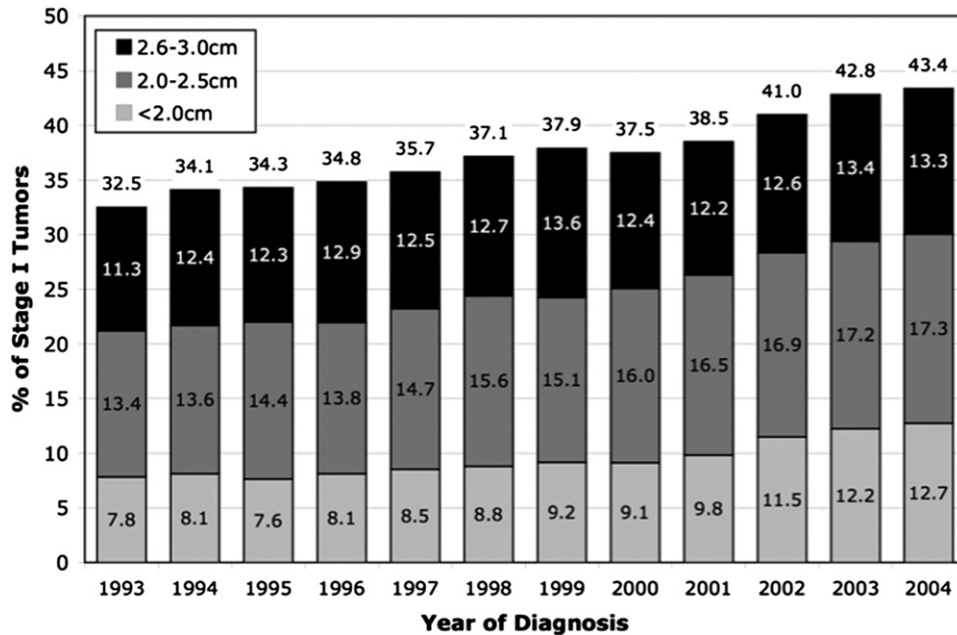


FIG. 2. Values above bars indicate total percent of stage I tumors 3 cm or less by diagnosis year

often than advanced, symptomatic tumors. However, Surveillance, Epidemiology and End Results data demonstrate an increase in kidney cancer specific mortality from 1.2 to 3.2/100,000 individuals from 1983 to 2002. This disconnect between increasing mortality rates and improved survival can be explained by an absolute increase in the incidence of advanced kidney cancer, and by lead time and length biases, which must be considered when interpreting the improvement in 5-year survival.³

Hock et al reported a population based analysis of the RCC incidence from 1973 to 1998 using data from the national Surveillance, Epidemiology and End Results registries.² They found an increasing incidence across all disease stages at diagnosis (localized, regional and distant) from 6.2 to 9.6/100,000 across the study period. They reported no

significant difference in stage distribution with time but this lack of significance was likely a result of a binary breakdown of time in the analysis, which compared data from 1973 to 1985 to data from 1986 to 1998 (45% vs 54% localized, $p = 0.45$). An analysis of trends over more finely divided time categories would likely have been significant. Indeed, the annual increase in the incidence of localized tumors was significantly higher than the annual increases in the incidence of regional and distant tumors (3.7% vs 1.9% and 0.7%, respectively, $p < 0.05$).² A prior analysis from the NCDB likewise demonstrated that stage I tumors represent a growing proportion of RCCs with a concomitant decrease in the proportion of all other tumor stages.⁴

Overall these epidemiological data question to an extent the intuitive presumption that early intervention for small

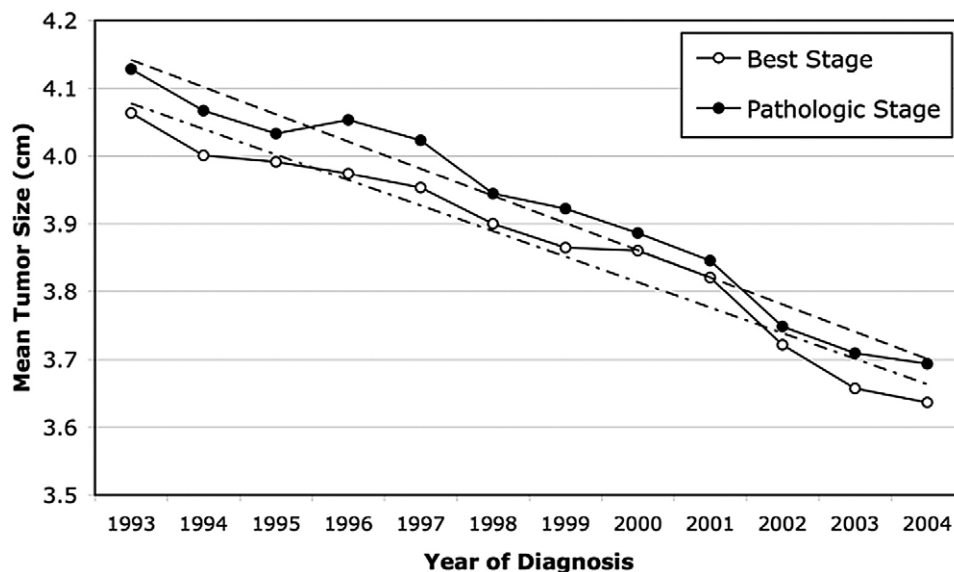


FIG. 3. Mean tumor size in stage I cases from 1993 to 2004 using best stage and pathological stage by diagnosis year. Trend lines were generated by simple linear regression with time.

RCCs should result in improved survival. It is possible that at least a subset of small masses would be characterized by an indolent course if left untreated. This possibility recalls the ongoing controversy regarding the optimal timing of intervention for low risk prostate cancer. Indeed, the published experience with observation for small enhancing renal lesions is limited but growing. A recent meta-analysis of 9 series showed that among 234 evaluable lesions the mean growth rate was 0.28 cm annually to a median followup of 32 months.⁷ Of 131 lesions with pathological data available 92% were confirmed to be RCC with a growth rate of 0.4 cm annually. While these data are reassuring and tend to support a large role for surveillance, some tumors grow more rapidly. Moreover, the growth rate cannot be predicted from size at diagnosis or other radiographic characteristics and rare cases of metastatic progression have been reported.⁷

As RCCs have trended toward smaller size at diagnosis, increasing attention has been given to other strategies for minimizing the impact of therapy in terms of overall morbidity and renal function. Academic studies consistently reflect an evolution from open radical nephrectomy to laparoscopy nephrectomy and open partial nephrectomy.^{8,9} Interest in laparoscopic partial nephrectomy, laparoscopic or percutaneous energy based ablation and observation is now likewise growing but these approaches are not universally accepted. Moreover, even in large series the potential complications of nephron sparing surgical treatments can be substantial.^{10–12} Limited community based data suggest an increasing uptake of minimally invasive and nephron sparing approaches to small renal lesions¹³ but practice patterns at the national level are not well characterized.

Ablative technologies offer the promise of decreased treatment morbidity but even the largest series are characterized by relatively short followup and a limited number of patients. Ablation by no means eliminates the risk of significant injury to the kidney and/or surrounding organs,¹⁴ and diagnosis relies on pretreatment biopsy if one is performed. These technologies are generally applied to smaller lesions. The mean tumor size of 2.5 cm in a recent report including cryoablation and radio frequency ablation cases is typical.¹⁵ The fact that in the current NCDB analysis the stage I tumor size assessed by best stage was consistently smaller than the size assessed by pathological evaluation supports a presumption that smaller masses are more likely to be ablated or observed without performing pathological study. Conversely in an analysis of all RCCs in the NCDB best stage tended to be slightly larger than pathological stage because large tumors associated with advanced stage may not undergo surgery.⁴

The most important limitation of this study is that the 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 tissue diagnosis. Of the 104,350 cases 102 and 213 have only radiographic or an unknown source of staging, respectively. The likelihood of benignity increases inversely with tumor size. A large series of 2,770 renal tumor resections during a 30-year period showed a rate of 12.8% benign tumors overall with 25% of the masses less than 3 cm, 30% of those less than 2 cm and 44% of those less than 1 cm found to be benign.¹⁶ Another recent series of 349 cases demonstrated that of enhancing renal masses benign

tumors accounted for 6.3% that were 7.0 cm or greater, 6.3% that were 4.0 to 6.9 cm, 17.5% that were 3.0 to 3.9 cm, 22.9% that were 2.0 to 2.9 cm and 27.9% that were less than 2.0 cm.¹⁷ Thus, the proportion of small masses of all enhancing renal masses is likely to be even greater than the proportion of small RCCs of all RCCs. The data underestimate the overall number of small enhancing renal masses and likely overestimate the average size of all enhancing masses. These results highlight a significant need for novel methodologies based on imaging, serology and/or biopsy that can predict lesion histology and the likelihood of progression.

CONCLUSIONS

Even as RCCs are more likely to be diagnosed at stage I, they are also decreasing in size at presentation in the group of stage I tumors. Based on 2004 NCDB data 43% of stage I tumors are now less than 3 cm at diagnosis. Conservative management strategies for small renal masses, including energy ablation and observation in select cases, are likely to increase in importance.

APPENDIX 1

More information on NCDB may be found at <http://www.facs.org/cancer/ncdb>.

APPENDIX 2

ICD-O-3 Code Histological Classification

8260 Papillary renal cell carcinoma
8310 Clear cell adenocarcinoma
8312 Renal cell carcinoma, not otherwise specified
8316 Cystic renal cell carcinoma
8317 Chromophobe renal cell carcinoma
8318 Sarcomatoid renal cell carcinoma

Surgery Code Procedure

20 Local tumor excision
30 Partial/subtotal nephrectomy
40 Total/simple nephrectomy
50 Radical nephrectomy
60 Nephrectomy with resection of other organs
80 Nephrectomy, not otherwise specified

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
ICD-O-3 = ICD for Oncology, 3rd edition
NCDB = National Cancer Data Base
RCC = renal cell carcinoma

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