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# Renal Cell Cancer Stage Migration

## *Analysis of the National Cancer Data Base*

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**BACKGROUND.** Evidence exists to suggest a pattern of increasing early diagnosis of renal cell carcinoma (RCC). The aim of the study was to analyze patterns of disease presentation and outcome of RCC by AJCC stage using data from the National Cancer Data Base (NCDB) over a 12-year period.

**METHODS.** The NCDB was queried for adults diagnosed between 1993 and 2004 presenting with ICD-O-2 of 3 renal cell tumors arising in the kidney. Cases were classified by demographics, 2002 AJCC stage (6th edition), and histology. The Cochran-Armitage Test for Trend was used to determine statistical significance of trends over time. Cox regression multivariate analysis was used to evaluate the impact of stage and histology on relative survival. SPSS 14.0 was used for analyses.

**RESULTS.** Between 1993 and 2004 a total of 205,963 patients from the NCDB fit our case definition of RCC. Comparisons between 1993 and 2004 data show an increase in stage I disease and decrease in stage II, III, and IV disease ($P \leq .001$). The size of stage I tumors also decreased from a mean of 4.1 cm in 1993 to 3.6 cm in 2003. In multivariate analysis, stage, but not histology, predicted relative survival. A 3.3% increase in survival was found for patients diagnosed in 1998 compared with patients diagnosed in 1993.

**CONCLUSIONS.** A greater proportion of newly diagnosed patients with RCC currently present with stage I disease compared with earlier years. Stage predicts relative survival for patients with kidney cancer. More recently diagnosed patients have improved relative survival. ***Cancer* 2008;113:78–83.** © *2008 American Cancer Society.*

**KEYWORDS: renal neoplasm, sex, epidemiology, mortality, National Cancer Data Base, stage migration.**

There will be approximately 51,190 new cases of renal cell carcinoma (RCC) in the US, with approximately 12,890 deaths in 2007.[1] Deaths due to kidney cancer account for about 3% of all cancer deaths in the US. Recent studies suggest that the incidence of RCC is increasing.[2,3] Although the largest increase is among early-stage, incidentally discovered tumors presumably detected through increased use of imaging, later-stage tumor incidence is increasing as well in both men and women.[4] The magnitude of stage migration toward lower stage at diagnosis and its impact on patient outcomes have not been well characterized.

The National Cancer Data Base (NCDB) currently includes approximately 19 million cases of reported cancer diagnosed between 1985 and 2004. By using the NCDB, we sought to assess whether or not stage migration has occurred and characterize its magnitude. In addition, we analyzed overall relative survival and stage-specific


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survival using the 1993 and 1998 cohorts to evaluate whether stage migration has led to improved relative survival.

## MATERIALS AND METHODS

The NCDB, a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, is a cancer management and outcomes database for healthcare organizations. It has been described in detail elsewhere.[5] The NCDB is a nationwide oncology dataset that currently captures approximately 75% of all newly diagnosed cancer cases from over 1400 facility-based cancer registries annually and holds information on over 19 million cases of cancer diagnosed between 1985 and 2004.

We queried the NCDB for adults (18 years and older) diagnosed between 1993 and 2004, presenting with renal cell tumors (coded ICD-O-2 of 3) arising in the kidney (C64.9), with histology codes 8260, 8310, 8312, 8316, 8317, 8318, and behavior code 3. (Histology codes in the NCDB are defined as follows: 8260, papillary; 8310, clear cell; 8312, RCC not otherwise specified [NOS]; 8316, cyst-associated RCC; 8319, RCC chromophobe type; 8318, RCC sarcomatoid. Behavior code 3 indicates malignancy.)

Both clinical and pathologic staging information were available in the database. Tumors were staged according to the sixth edition of the AJCC,[6] using AJCC pathologic stage group, supplemented by AJCC clinical stage group when pathologic stage was not recorded. Cases diagnosed before the implementation of the sixth edition were restaged using the sixth edition criteria. Cases missing stage information were excluded. Significance of trends in stage distribution over time was assessed with the Cochran-Armitage chi-square test for trend.

Five-year relative survival was calculated for all stages combined, for each stage, and for the 3 major histologies analyzed (renal cancer NOS, clear cell, and papillary adenocarcinoma). Observed survival in months was calculated using death from any cause as the outcome. Relative survival is the ratio of the observed survival rate to the expected survival rate, adjusted for age, sex, race, and Hispanic origin. Expected survival rates are based on the 1990 life expectancy tables from the National Cancer Institute.[7] A multivariate Cox proportional hazards model[8] was performed examining the impact of age, race/ethnicity, stage, and histology on relative survival. Analyses were performed with SPSS v. 14.0 (Chicago, Ill) and SAS v. 9.1 (Cary, NC) for Cochran-Armitage trend tests.

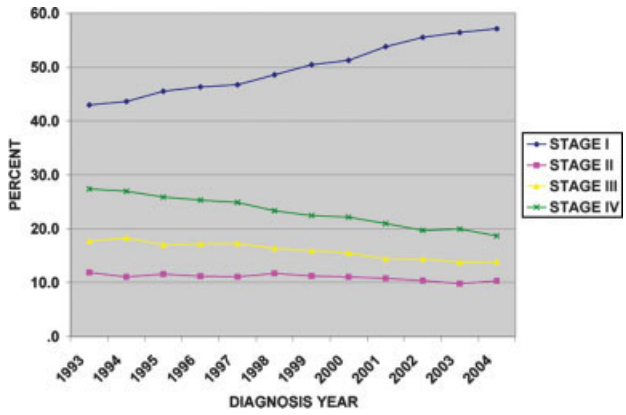


**FIGURE 1.** Renal cell carcinoma (RCC) stage distribution by diagnosis year.

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 CoC-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 reported in the Standards for Privacy of Individually Identifiable Health Information, Final Rule (45 CFR Parts 160 and 164).

## RESULTS

Between 1993 and 2004 a total of 236,975 patients from the NCDB fit our case definition of RCC. Of these, 31,012 were missing stage information (13.1%), resulting in 205,963 patients available for analysis. The age, sex, ethnicity, and histology of the patients without stage information are similar to those of patients with stage information (data not included). A total of 104,214 (50.6%) were stage I, 55,002 (26.7%) were stage II or III, and 46,747 (22.7%) were stage IV. Figure 1 demonstrates a downward stage migration over the 12-year period, with increasing representation of stage I tumors and decreasing proportions of stage II, III, and IV disease, with a significant ($P < .001$) test for trend for each stage of disease. Between 1993 and 2004 the proportion of stage I cases increased from 43.0% to 57.1%, whereas

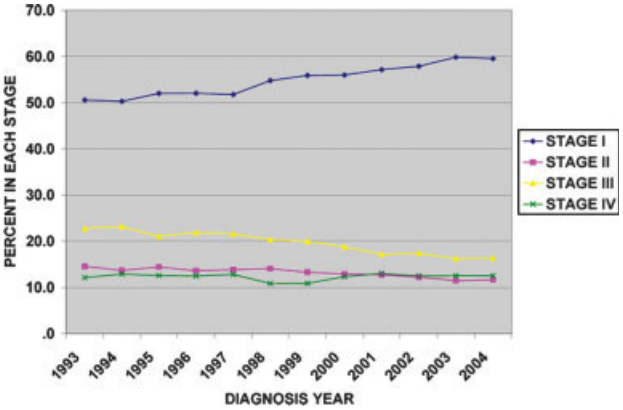


**FIGURE 2.** Renal cell carcinoma (RCC) pathologic stage distribution by diagnosis year.

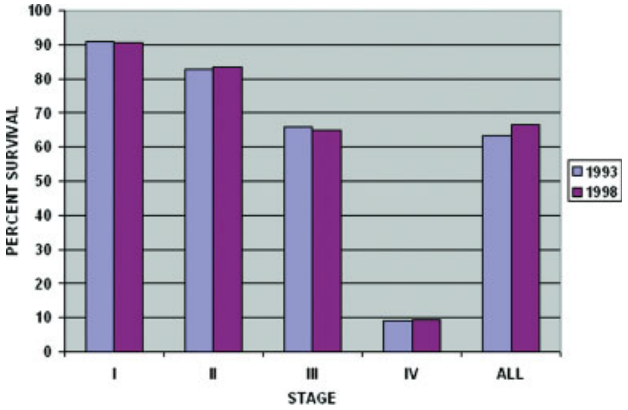


**FIGURE 3.** Renal cell carcinoma (RCC) 5-year relative survival by stage for 1993 and 1998 cohorts.

**TABLE 1**
**Stage Percentage Distribution by RCC Histology 1993–2004***

| Histology group | Stage I | Stage II | Stage III | Stage IV | Total no. (%)† |
|---|---|---|---|---|---|
| RCC NOS | 49.0 | 10.9 | 16.0 | 24.1 | 160,435 (77.9) |
| Clear cell | 54.7 | 10.6 | 16.1 | 18.6 | 33,137 (16.1) |
| Papillary | 68.0 | 11.5 | 11.2 | 9.3 | 7104 (3.4) |
| Chromophobe | 65.6 | 18.8 | 10.8 | 4.8 | 2975 (1.4) |
| Sarcomatoid | 9.0 | 6.4 | 21.8 | 62.8 | 1648 (0.8) |
| Cyst-associated | 83.0 | 9.6 | 4.2 | 3.2 | 664 (0.3) |
| All histologies | 50.6 | 10.9 | 15.8 | 22.7 | 205,963 (100.0) |

RCC indicates renal cell cancer; NOS, not otherwise specified.
* Cyst-associated, chromophobe, sarcomatoid from 2000–2004 only.
† Excludes 31,012 with missing stage information.

the proportion of stage IV tumors decreased from 27.4% to 18.7%. The proportion of stage II and III cases also declined in the 12-year period, from 11.9% to 10.3% and from 17.7% to 13.9%, respectively. This evidence suggests that all cases are migrating from later stages to earlier stages over the period of observation. The size of stage I tumors also decreased from a mean of 4.1 cm (95% confidence interval [CI], 4.0–4.1) in 1993 to a mean of 3.6 cm (95% CI, 3.6–3.7) in 2004.

Figure 2 shows the migration to pathologic stage I from higher stages in surgical patients that had complete pathologic information for review (surgery codes 20-80) for diagnosis years 1993–2004. The percentage increase from 50.6% in 1993 to 59.5% in 2004 represents a statistically significant increase in stage I disease over the 12-year period (trend test, $P < .001$). Pathologic stage II disease decreased from 14.5% in 1993 to 11.6% in 2004 (trend test, $P < .001$), whereas pathologic stage III disease showed a larger decline from 22.8% in 1993 to 16.3% in 2004 (trend test, $P < .001$). Pathologically staged IV disease remained relatively constant throughout the 12-year period (trend test, $P > .25$).

Table 1 examines histology by best stage. Our ability to examine the impact of histology on stage is limited by 2 factors. First, a specific histology code was not listed for most patients; rather, most (78%) were coded as RCC NOS. Second, cyst-associated, chromophobe, and sarcomatoid codes have been recorded in the NCDB only since 2000. Clear cell carcinoma, papillary adenocarcinoma, cyst-associated, and chromophobe RCC patients are most commonly diagnosed at stage I. In contrast, 84.6% of those with sarcomatoid histology presented with stage III or IV disease.

Relative survival was calculated for all stages combined, for each stage, and for the 3 major histology groups by comparing the overall survival of each cohort to age- and sex-adjusted predicted survival. The median follow-up for the 1993 and 1998 cohorts was 70.3 months and 73.7 months, respectively ($P < .001$ by log-rank test). For all stages combined, survival for patients diagnosed in 1998 (66.6%, 95% CI, 65.6–67.6) was slightly higher than for patients diagnosed in 1993 (63.3%, 95% CI, 62.2–64.4). For patients diagnosed in 1998, 5-year relative survival by stage was 90.7% for stage I, 83.5% for stage II, 64.9% for stage III, and only 9.5% for stage IV. Five-year stage-specific survival for patients diagnosed in 1998 was similar to 1993 stage-specific survival, with no significant differences within any stage (Fig. 3). On multivariate analysis examining the impact of age, stage, and histology on relative survival for patients diagnosed in 1993–1998, stage was a strong, independent predictor of survival, whereas histology was not, although clear cell carcinoma cases showed a slight survival advantage (Table 2). Age was also a strong predictor of survival in this model.

**TABLE 2**
**Results of Multivariate Analysis of Impact of Stage, Histology Code, and Age Group on Relative Survival for Cases Diagnosed in 1993–1998***

| Variable | No. | Hazard ratio | 95% CI | *P* |
|---|---|---|---|---|
| Stage | | | | <.001 |
| I | 40,343 | 1.00 | | |
| II | 10,067 | 1.22 | 1.17–1.27 | |
| III | 15,235 | 2.02 | 1.96–2.08 | |
| IV | 22,463 | 10.56 | 10.30–10.82 | |
| Histology | | | | |
| RCC NOS | 77,862 | 1.00 | | <.001 |
| RCC clear cell | 9845 | 0.85 | 0.82–0.88 | <.001 |
| RCC papillary | 401 | 1.05 | 0.91–1.21 | .51 |
| Age group, y | | | | <.001 |
| 18–59 | 32,021 | 1.00 | | |
| 60–69 | 24,882 | 1.30 | 1.27–1.34 | |
| 70–79 | 23,332 | 1.80 | 1.76–1.85 | |
| 80 and older | 7873 | 2.64 | 2.56–2.73 | |

CI indicates confidence interval; RCC, renal cell cancer; NOS, not otherwise specified.
* Total number of cases with nonmissing data is 88,108.

## DISCUSSION

The incidence of RCC is increasing, at least partially because of the increased use of abdominal imaging.[2,3] Single-institution series have demonstrated an increased number of incidentally discovered tumors,[9] which tend to be smaller, of a lower stage, and associated with improved cancer-specific survival.[10] Hock et al.[3] analyzed Surveillance Epidemiology and End Results (SEER) data on RCC between 1973 and 1998, finding an increase in all stages of the disease and no evidence of changing stage at presentation. However, the negative finding with respect to stage migration may have been an artifact of how the authors defined the time groups in their analysis. Indeed, more recently Hollingsworth et al.[11] analyzed the SEER database and noted that most of the increased incidence of kidney cancer cases appears to be from low-stage disease. However, despite increased detection and treatment, mortality from kidney cancer appears to be increasing.

The stage migration pattern that is evident from the present analysis is striking and more significant than expected. Stage I RCC increased from approximately 43% to 57% of new patients between 1993 and 2004. If we include only surgically staged patients, stage I renal cell carcinoma patients increased from 51% to 60% between 1993 and 2004. There was a concomitant decrease in the proportion of all other stages of disease during the same time interval. The reason for the profound stage migration is likely the increased and widespread use of cross-sectional imaging.[12] Chow et al.[2] proposed that the reason for the increase in incidence noted in the US and Europe[4] is the use of imaging. Others have shown that incidentally detected masses are more likely to be benign, smaller,[13] and—when confirmed to be kidney cancer—to have better rates of survival.[14] The improved cancer-specific survival of incident cases has not, thus far, resulted in a decrease in mortality from kidney cancer and may be because of lead-time and length biases.[11] The growth rate of renal masses is highly variable,[15] however, and the time interval between effective treatment and benefit from a survival perspective may be very long, especially for small, incidentally discovered masses.

Pathologic and clinical staging may yield different results because tumors tend to be larger on imaging than their ultimate size when measured pathologically.[16,17] Within the NCDB, the surgical patients are staged pathologically. When analyses are performed for the entire cohort, 'best stage' is used, which refers to clinical staging for nonsurgical patients and pathologic staging for surgical patients. This may introduce some bias because of subtle size differences between clinical and pathologic staging. Including all patients, best stage will also tend to be smaller than pathologic stage because some patients with advanced disease associated with larger tumors *do not* undergo surgery. Among those with stage I–only tumors, conversely, smaller tumors are more likely to be ablated with cryotherapy or radiofrequency energy; thus, pathologic stage will tend to be higher than best stage.

The robustness of the histology information in the NCDB is limited but improving over time. It depends on the histology being properly recorded by the tumor registry at the participating institutions. Unfortunately, 78% of the patients with kidney cancer in this analysis were classified as RCC NOS. This high proportion of nonspecific histology precludes careful examination of the proportion of specific histology by stage and limits a robust examination of the impact of histology on outcome. The slight survival advantage found among patients with clear cell histology as compared with RCC NOS was confined to stage III-IV patients (data not shown). We hypothesize that sarcomatoid histologies might be found in the stage III-IV RCC NOS categories and, because they have poorer survival, may be driving the differences with clear cell and RCC NOS. Our finding that histology is not an independent predictor of outcome supports the work of others.[18] The histology classification system changed in 1997[19] and may have impacted the coding of particular histology subtypes before 1997, and the integration of the new system has likely been variable between regions and centers since.

The 5-year relative survival for patients with kidney cancer diagnosed between 1993 and 1998 was 90.4% for stage I, 83.4% for stage II, 66.0% for stage III, and 9.1% for stage IV (Fig. 3). This is quite similar to the cancer-specific survival for stages I-III calculated for surgically treated patients from large, single-institution series.[20] Relative survival may underestimate cancer-specific survival, however, because patients undergoing therapy for kidney cancer may be more prone to renal insufficiency than an age-, sex-, and ethnicity-matched cohort. The very low 5-year relative survival noted in our NCDB series for stage IV patients is also consistent with other large, single-institution series.[21]

A small, statistically significant improvement in 5-year relative survival was detected for the 1998 cohort as compared with patients diagnosed in 1993. Because there were no significant improvements in stage-specific survival for these 2 cohorts, the small improvement in survival is likely related to the decrease in the proportion of stage II and III patients in 2004 (32.6%) compared with 1998 (39.7%) and 1993 (45.1%).

It is interesting that the proportion of surgically staged patients with stage IV disease remained relatively constant at 11% to 13% across the era of review. Presumably this represents cytoreductive nephrectomy performed for patients with known metastatic disease and nephrectomy performed on patients discovered to have stage IV disease at the time of surgery. Most of the patients in this analysis were cared for before the recent evidence suggesting the value of cytoreductive nephrectomy before systemic therapy.[22]

Although the stage migration noted in this database is profound, the impact of widespread imaging on detection of small renal masses is not measured in full, as only those with RCC were analyzed. Not all those with incidentally discovered masses have RCC. For a patient with an incidentally discovered solid renal mass, the likelihood of kidney cancer histologically is related to the size of the mass on imaging. For masses under 2 cm in diameter, as many as 25% are benign on final histology[23]; therefore, the size migration of masses that require intervention is greater than the stage migration of histologically proven RCC seen in this analysis. The improvement in survival of the entire cohort is therefore most likely due to the migration to a greater proportion of newly diagnosed patients being diagnosed and treated when their kidney cancer is small. The proportion of these small kidney cancers that were destined to progress is unknown. The value of screening imaging is unproven and depends on the cost of the test, the prevalence and lethality of the disease, and the age and comorbidity of the screened population.

There are limitations to the current study. Although the NCDB is robust, it does not sample a representative section of the entire population; therefore, incidence and prevalence data cannot be derived. Also, the precision of the information depends on the quality of tumor registry data entered. Errors in staging can occur. No central pathology review or central case review for staging accuracy was performed. Despite these limitations, this is the largest multicenter database analysis of kidney cancer stage migration yet performed.

## Conclusions

A greater proportion of newly diagnosed patients with RCC currently present with stage I disease compared with the early 1990s. Stage I tumors have been getting smaller over the past 10 years. A small increase in relative survival was detected between 1993- and 1998-diagnosed cohorts. In multivariate analysis, stage and age are significant predictors of relative survival for patients with kidney cancer.

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