Effect of Reclassification on the Incidence of Benign and Malignant Renal Tumors

Ted A. Skolarus,*,† Maria F. Serrano,* Robert L. Grubb, III,‡ Matthew D. Katz,* Travis L. Bullock,§ Feng Gao,* Peter A. Humphrey* and Adam S. Kibel‖

From the Division of Urologic Surgery, Department of Surgery (TAS, RLG, MDK, TLB, ASK), Department of Pathology and Immunology (MFS, PAH), Division of Biostatistics (FG), and Alvin J. Siteman Cancer Center (RLG, FG, PAH, ASK), Washington University School of Medicine and Barnes Jewish Hospital, St. Louis, Missouri

Purpose: The incidence of benign renal tumors has increased in recent years. This trend is commonly attributed to the increased use of cross-sectional imaging and minimally invasive surgical approaches. An alternative hypothesis is that recent changes in histological classification are responsible for the increasing incidence. To further investigate the impact of histological reclassification we reexamined all excised renal masses using the 2004 WHO criteria and compared this histological classification to the prior criteria.

Materials and Methods: We identified 1,101 consecutive partial and radical nephrectomy cases managed at our institution from 1989 to 2003. All histopathological sections were rereviewed by a single pathologist and reclassified according to 2004 WHO criteria. The percentages of benign lesions per year according to the prior histological and current WHO 2004 histological criteria were compared.

Results: Of the 1,101 renal masses 132 (12.0%) and 165 (15.0%) were classified as benign using prior and current WHO criteria, respectively. On average the WHO criteria diagnosed more benign tumors per year than the prior criteria ($p = 0.004$). Linear regression demonstrated a similar, persistent increase in benign diagnoses per year of 0.69% (WHO) and 1.22% (prior) during the 14-year period ($p = 0.33$). All masses reclassified as benign were oncocytoma (33).

Conclusions: Implementation of the 2004 WHO criteria is contributing to the increase in diagnosis of benign renal lesions, specifically oncocytoma. Changes in histological classification do not account for the entire increase. Other factors, which remain to be delineated, are also contributing to the increase in the diagnosis of benign renal lesions.

Key Words: kidney neoplasms, histology, nephrectomy, pathology

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Study received institutional review board approval.

* Nothing to disclose.

† Correspondence: Division of Urologic Surgery, Washington University in St. Louis, 4960 Children's Place, Box 8242, St. Louis, Missouri 63110 (telephone: 314-362-8212; e-mail: skolarust@wudosis.wustl.edu).

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ACCORDING to Surveillance, Epidemiology, and End Results data there is an increasing incidence of renal cell carcinoma in men and women.[1] This increasing incidence can be attributed to several factors including the increased use of cross-sectional imaging[1,2] and the widespread implementation of laparoscopic nephrectomy.[3–7] These factors have led to the increased detection and extirpation of asymptomatic renal masses,[8,9] which are more likely to be smaller and to have a benign histopathological diagnosis.[10,11]

While the effects of these trends have been well documented, the effect of histological classification on the incidence of benign renal tumors has been less well explored. The distribution of benign and malignant renal tumors is determined by histological classification.[12,13] Thus, the World Health Orga-

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nization recently updated its histological classification system to reflect an improved understanding of the genetic basis of renal pathology.[12] Several histological subtypes were eliminated, and in some cases previously designated malignant tumors such as granular renal cell carcinoma and renal cell carcinoma of oncocytic type were reclassified as benign.[14] Although the widespread adoption of this reclassification can be expected to lag behind its introduction, we hypothesized that the increasing incidence of benign renal tumors may be partly a consequence of the implementation of the 2004 WHO histological criteria.[15] To test our hypothesis we reviewed all surgically excised renal masses at Barnes-Jewish Hospital during a 14-year period and reclassified them according to the 2004 WHO histological criteria. Furthermore, we measured the extent to which reclassification affected the incidence of surgically removed benign renal tumors.

MATERIALS AND METHODS

Study Population

After obtaining institutional review board approval we retrospectively reviewed the clinical and pathological data from all patients with renal masses treated with radical or partial nephrectomy for suspected renal carcinoma from 1989 through 2003 at Barnes-Jewish Hospital. The Barnes-Jewish Hospital Oncology Data Services maintains an American College of Surgeons Commission on Cancer approved database of all patients with cancer treated at our institution. Tumor registrars prospectively collect data on the date of diagnosis, demographic information, and stage, grade and nodal status at presentation. Additionally, the dates and types of initial and secondary treatments as well as current disease status are collected.

Histological Classification

The prior histological classification for each renal tumor was determined by review of the original clinical pathology report. The original clinical pathology reports spanned the entire study interval and, therefore, represented a variety of prior histological classification schemes. A single pathologist (MFS) rereviewed all surgical specimens using the 2004 WHO classification scheme. Histopathological sections stained with hematoxylin and eosin were examined using standard light microscopy. In addition, variables such as tumor stage, Fuhrman grade and size were assessed during pathological rereview. Based on study criteria we excluded from analysis patients with upper tract urothelial carcinoma (98), original tumor pathology not available (2) and B-cell lymphoma (1).

Statistical Analysis

To better understand if the annual incidence of benign renal tumors during our study period differed using the prior vs the current histological (WHO) classification schemes we used a paired Student's t test. To measure the change in the percentage of benign tumors over time for each classification scheme, a weighted linear regression model (weighted by the variances of the corresponding pooled point estimate at each year) was fitted.[16] A z statistic was used to discern a trend difference for benign prior and WHO diagnoses. The weighted linear regression models were fitted using Joinpoint Regression Program version 3.0 (http://srab.cancer.gov/joinpoint/, Statistical Research and Applications Branch, National Cancer Institute) while the other statistical analyses were performed using SAS® statistical package version 9.1. All p values were 2-tailed and the probability of a Type I error was set at 0.05. All masses were included in the statistical analysis.

RESULTS

Among the 1,101 renal masses 358 (32.5%) diagnoses were reclassified using the 2004 WHO criteria. With respect to benign tumors 132 (12.0%) and 165 (15.0%) were classified as benign using the prior and WHO criteria, respectively ($p = 0.004$). For malignant tumors a total of 325 were reclassified and maintained malignant status with no previously benign tumors classified as malignant. Figure 1 portrays the frequency of benign tumors by year according to the compared histological criteria. Overall the total number of excised renal tumors per year (not including upper tract urothelial carcinoma) ranged from 32 in 1990 to 152 in 2003.

All newly classified benign tumors were oncocytomas (33) with the prior malignant types shown in the table. The most common change of classification was for those patients with renal cell carcinoma with oncocytic features (12). There was no tumor recurrence at a median followup of nearly 9 years (range 0 to 15) for 24 of the 33 patients with available followup data. One patient did have a contralateral renal mass biopsied which revealed oncocytoma. Other benign tumors based on 2004 WHO and prior criteria did not change, indicating an otherwise consistent benign histological classification between the 2 schemes in cases of benign

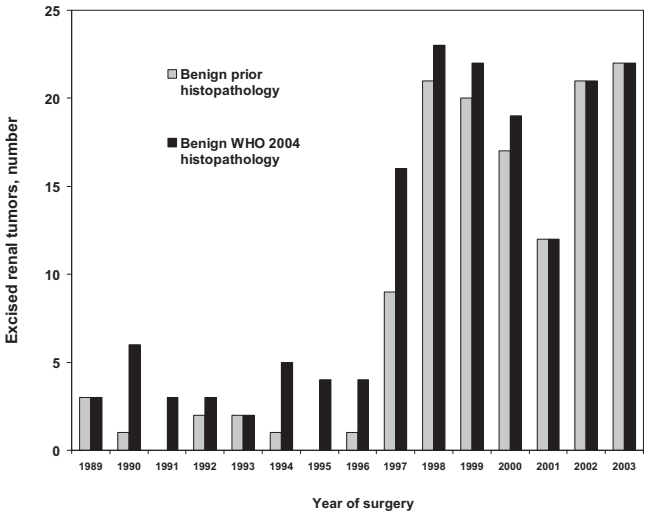

Figure 1. Frequency of benign tumors by year

Reclassified histology of benign renal tumors

WHO 2004 Reclassification[12]	Prior Classification (No.)
Oncocytoma (33)	Renal cell Ca with oncocytic features (12)
	Renal cell Ca, oncocytic type (9)
	Renal cell Ca, granular cell type (5)
	Renal cell Ca, oncocytoid type (4)
	Renal oncocytoid neoplasm (1)
	Renal cell Ca, clear cell type (1)
	Renal cell Ca, type not specified (1)

cyst (43), angiomyolipoma (40), leiomyoma (3), cystic nephroma (1) and medullary fibroma, ie renomedullary interstitial cell tumor (1).

On average the use of the 2004 WHO criteria resulted in more benign tumors per year than the prior criteria ($p = 0.004$). Linear regression analysis demonstrated a persistent increase in benign diagnoses of 0.69% per year for the 2004 WHO criteria and 1.22% per year for the prior criteria during the 14-year period (fig. 2). There was no significant difference between the corresponding slopes of the prior vs 2004 WHO diagnostic schemes ($p = 0.33$), indicating that both schemes had a similar increasing incidence of surgically excised benign renal tumors during the period studied.

DISCUSSION

This study demonstrates an increasing incidence of benign neoplasms in surgically excised renal masses at our institution. This increasing incidence was present using the prior and 2004 WHO histological typing schemes during the 14-year period. Using the 2004 WHO histological scheme an additional 33 tumors previously classified as malignant (eg renal cell carcinoma) were reclassified as oncocytomas, significantly increasing the number of benign renal tumors ($p = 0.004$). Thus, the implementation of the 2004 WHO criteria is contributing to an increase in the annual incidence of benign tumors at our institution. However, these data indicate an increase in benign, surgically excised tumors in the last decade regardless of which histological typing system is used.

Since current practice remains to surgically excise the majority of solid renal masses, the increasing incidence of benign renal tumor pathology has clinical implications. Aggressive treatment of an increasing proportion of benign tumors places patients at risk for adverse treatment consequences without the benefit of curing the malignancy. The median age of patients in our study later found to have oncocytoma was 71 years (range 41 to 85). These older patients faced an increased surgical risk for the resection of benign tumors. Furthermore, as active surveillance of renal masses becomes more common, the natural history of unresected, typically smaller tumors will be better understood.[17] However, at present it can be difficult to accurately determine if an oncocytic tumor is malignant or benign without surgical excision. While needle biopsies are advocated,[18] hybrid oncocytoma-renal cell carcinoma cases do exist,[19] suggesting caution in diagnosing pure oncocytoma on needle biopsy. Improvements in pathological/molecular tissue analysis and/or imaging are needed, which would potentially allow clinicians to spare some patients the morbidity of aggressive treatment for lesions that are likely benign.

Alternative explanations for the increasing incidence of benign renal tumors are 1) increased detection of small renal masses that are more likely to be benign due to the increased use of cross-sectional imaging,[1,2,10,11,20] 2) more frequent excision of small, solid renal tumors due to the increased use of laparoscopy[3–7] and 3) a true increase in the incidence of benign renal tumors. It is likely that all of these factors in addition to the implementation of a new histological classification scheme are contributing to the increasing incidence of benign renal tumors.

Although the 2004 WHO criteria represent the most up-to-date classification scheme, changing pathological clinical practice to reflect current consensus has many barriers which result in delayed adoption.[15] In the past some oncocytomas were classified as renal cell carcinomas of oncocytic type.[21] Several tumors in our study classified as granular renal cell carcinoma or renal cell carcinoma of oncocytic type would now be classified as oncocytoma. However, as expected, no recurrent renal cell carcinomas were detected in evaluable patients whose tumors were reclassified as oncocytoma during a nearly 9-year period. Thus, adoption of the 2004 WHO histological classification scheme and recognition that

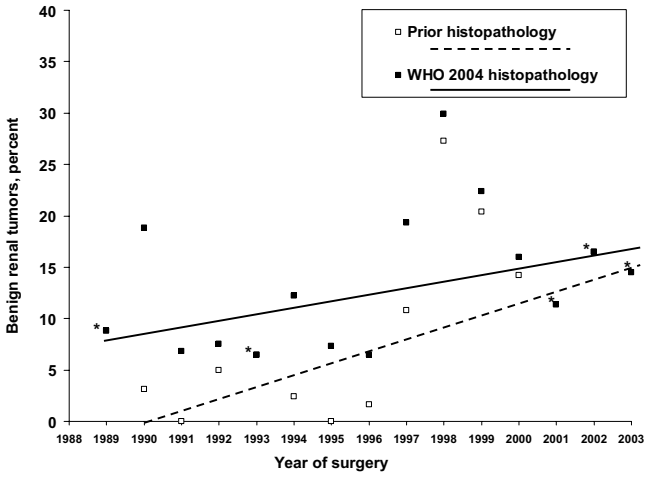

Figure 2. Linear regression analysis showing persistent increase in benign diagnoses of 0.69% per year for 2004 WHO criteria and 1.22% per year for prior criteria. Asterick indicates same percent of benign renal tumors for both histological schemes.

previous classifications of granular cell renal cell carcinoma and oncocytic renal cell carcinoma may represent oncocytoma in some cases by the 2004 WHO scheme, are important concepts in eliminating unnecessary followup for patients with benign renal tumors.

Although the uniform reclassification of this large consecutive series of renal masses adds to the strength of the study, it remains limited because it is retrospective and represents a single institutional experience. A lack of pathological consensus among several reviewers may also be of concern. However, interobserver consensus in globally discerning benign vs malignant renal tumors as performed in this study is high compared to further tumor subtyping.[22] This study demonstrates the increasingly benign nature of surgically excised renal masses at a tertiary referral center and, thus, the findings may not be generalizable to a broader population due to potential selection bias. In addition, recurrence data were not available in 9 of the 33 cases in which a new classification of oncocytoma was made. However, in those cases with followup data no malignant recurrence was noted. Finally categorizing all radiographically diagnosed renal masses, resected and observed, would provide further insight into benign renal tumor trends. However, the limitations of accurately diagnosing oncocytoma preoperatively, using needle biopsy or radiographic means, especially in the case of hybrid morphology, will continue to limit our true understanding of benign disease incidence.[17,19,23–25]

The implications of our findings affect pathologists, urologists, radiologists, oncologists and patients. Future retrospective studies on the incidence of benign renal tumors should consider tumor pathology review using a consistent histological scheme. Use of the 2004 WHO classification scheme for renal neoplasms will allow for improved postoperative followup for patients, especially those with benign disease.

CONCLUSIONS

Implementation of the 2004 WHO criteria is contributing to the increasing incidence of benign renal tumors, specifically oncocytoma. However, other as yet unexplained factors are also contributing to the increase in diagnosis. As treatment options for renal masses expand, understanding the distribution of benign tumors will become increasingly important to guide clinical decision making. Accurate histological classification is necessary to provide the most appropriate care for patients after surgical removal of renal masses.

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EDITORIAL COMMENT

Following radical or partial nephrectomy postoperative management is highly dependent on the pathological evaluation of the excised specimen. Pathological data provide important prognostic information for patients with malignant tumors, and liberate those patients from concerns about recurrent disease for concern about benign tumors. The classification of renal tumors has undergone a rapid evolution with multiple changes in recent decades. The present study demonstrates that implementation of the 2004 WHO criteria resulted in a greater number of benign renal tumors compared to prior classification schemas.

In this study the annual incidence of benign tumors increased from 6 or less before 1997 to approximately 20 after 1997 regardless of the classification schema. However, the use of the 2004 WHO criteria likely had a small role in the well documented increasing incidence of benign renal tumors. The changing epidemiology of renal tumors is more likely due to the increase in management of small renal masses because tumor size is one of the most important predictors of benign disease (references 9 and 20 in article).[1]

Nevertheless, the authors present a compelling argument for the expeditious adoption of new histological classification criteria. It is worthwhile even if a small group of patients can avoid expensive followup costs, radiation exposure and unnecessary concern about tumor recurrence. To provide the best patient care advances in imaging are needed to better characterize renal masses, and someday it may be possible to accurately define tumor biology using molecular classification.

Steven L. Chang and Mark L. Gonzalgo
Department of Urology
Stanford University School of Medicine
Stanford, California

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REPLY BY AUTHORS

We agree that renal mass size is a predictor of tumor type. The increasing detection and resection of small renal masses are clearly contributing to the number of benign tumors. However, at our institution changes in histological classification also increased the number of benign lesions per year, especially before 1997 (fig. 1). Regardless of histological classification, an increasing percentage of benign diagnoses occurred (fig. 2). The point is that we need to better characterize renal tumors after surgery as we have shown, ideally before intervention to avoid the consequences of unnecessary care.