

# Preoperatively Misclassified, Surgically Removed Benign Renal Masses: A Systematic Review of Surgical Series and United States Population Level Burden Estimate

David C. Johnson,\* Josip Vukina, Angela B. Smith, Anne-Marie Meyer, Stephanie B. Wheeler, Tzy-Mey Kuo, Hung-Jui Tan, Michael E. Woods,† Mathew C. Raynor,‡ Eric M. Wallen, Raj S. Pruthi and Matthew E. Nielsen§

From the Departments of Urology (DCJ, JV, ABS, MEW, MCR, EMW, RSP), Epidemiology (AMM) and Health Policy and Management (SBW) and Lineberger Comprehensive Cancer Center (ABS, AMM, SBW, TMK, MEW, EMW, RSP), University of North Carolina (MEN), Chapel Hill, North Carolina, and Department of Urology, Robert Wood Johnson Clinical Scholars Program, University of California-Los Angeles (HJT), Los Angeles, California

#### Abbreviations and Acronyms

BRM = benign renal mass  
RCC = renal cell carcinoma  
RMB = renal mass biopsy  
SEER = Surveillance, Epidemiology and End Results  
SRM = small renal mass

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\* Correspondence: 2107 Physician's Office Building, Campus Box 7235, Chapel Hill, North Carolina 27599 (telephone: 919-966-8217; FAX: 919-966-0098; e-mail: dcjohnso@unch.unc.edu).

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Supplementary references 31 to 55 for this article can be obtained at <http://jurology.com/>.

For another article on a related topic see page 318.

**Purpose:** A significant proportion of renal masses removed for suspected malignancy are histologically benign with the probability inversely proportional to lesion size. To our knowledge the number of preoperatively misclassified benign renal masses treated with nephrectomy is currently unknown. Given the increasing incidence and decreasing average size of renal cell carcinoma, this burden is likely increasing. We estimated the population level burden of surgically removed, preoperatively misclassified benign renal masses in the United States.

**Materials and Methods:** We systematically reviewed the literature for studies of pathological findings of renal masses removed for suspected renal cell carcinoma based on preoperative imaging through July 1, 2014. We excluded studies that did not describe benign pathology and with masses not stratified by size, and in which pathology results were based on biopsy. SEER data were queried for the incidence of surgically removed renal cell carcinomas in 2000 to 2009.

**Results:** A total of 19 studies of tumor pathology based on size met criteria for review. Pooled estimates of the proportion of benign histology in our primary analysis (American studies only and 1 cm increments) were 40.4%, 20.9%, 19.6%, 17.2%, 9.2% and 6.4% for tumors less than 1, 1 to less than 2, 2 to less than 3, 3 to less than 4, 4 to 7 and greater than 7, respectively. The estimated number of surgically resected benign renal masses in the United States from 2000 to 2009 increased by 82% from 3,098 to 5,624.

**Conclusions:** These estimates suggest that the population level burden of preoperatively misclassified benign renal masses is substantial and increasing rapidly, paralleling increases in surgically resected small renal cell carcinoma. This study illustrates an important and to our knowledge previously unstudied dimension of overtreatment that is not directly quantified in contemporary surveillance data.

**Key Words:** kidney; carcinoma, renal cell; neoplasms; diagnostic errors; SEER program

THE incidence of RCC has increased in recent decades almost 3% annually from 1975 to 2007.<sup>1</sup> This steady increase is multifactorial but potentially due in large part to increased use of imaging modalities.<sup>2-5</sup> Currently most RCC cases are incidentally discovered during abdominal imaging.<sup>6,7</sup> Paralleling this increased incidence is stage migration resulting from a disproportionate increase in smaller RCCs and decreasing average tumor size at diagnosis.<sup>8-10</sup> SRMs, defined as tumors less than 4 cm, now comprise most incidentally detected solid renal lesions.<sup>6,7</sup> Intriguingly this increased detection of RCC and stage migration has not translated into decreased mortality.<sup>2,5,11,12</sup> These data suggest that the growing disconnection between RCC incidence and mortality may in part be the result of increasing over diagnosis and overtreatment of clinically insignificant disease, a trend observed at other cancer sites, including breast, melanoma, thyroid and prostate.<sup>12</sup>

However, less well appreciated is the impact of preoperatively misclassified BRMs. In contrast to most other tumor sites, it is within the standard of care to resect radiographically suspicious renal masses without a tissue diagnosis.<sup>13-15</sup> However, radiographically suspicious renal masses may in fact represent histologically benign mimickers of RCC and surgical series suggest that the frequency of this phenomenon is inversely proportional to lesion size.<sup>16</sup> Therefore, the current standard of care results in removal of a number of BRMs, exposing patients to potentially preventable and unnecessary morbidity. The unnecessary surgical removal of BRMs represents an important dimension of overtreatment that may be overlooked by current cancer surveillance data.<sup>12</sup> The data address overtreatment of clinically insignificant RCC rather than surgical removal of pathologically benign masses that were suspicious for RCC preoperatively.

Currently to our knowledge no population level data are available that directly measure this phenomenon. However, based on the evolving epidemiology of RCC and the relationship between lesion size and the likelihood of benign disease we hypothesized that there may be a significant and increasing burden of surgically resected, preoperatively misclassified BRMs. We systematically reviewed the literature to determine benign pathology rates in nephrectomy specimens obtained for suspected malignancy and estimated this population level burden of surgically resected BRMs in the U.S. as well as trends in the last decade.

## MATERIALS AND METHODS

### Data Sources

In collaboration with a health sciences research librarian we systematically searched MEDLINE®, Embase®,

Web of Science™ and The Cochrane Library for English language reports published from January 1, 1970 until July 1, 2014. MEDLINE search was done using combinations of MeSH (Medical Subject Headings) search terms and key words according to the algorithm, (“kidney neoplasms/surgery”[mesh] OR “nephrectomy”[mesh] OR “carcinoma, renal cell/surgery”[mesh] OR (“renal mass” AND surgery) OR (“renal masses” AND surgery)) AND (“kidney neoplasms/pathology”[mesh] OR “kidney neoplasms/epidemiology”[mesh] OR “carcinoma, renal cell/pathology”[mesh] OR pathology[mesh] OR histopathology OR pathological OR pathologic OR benign) AND (“prevalence”[Mesh] OR “incidence”[mesh] OR “tumor burden”[mesh] OR “odds ratio”[mesh] OR “incidental findings”[mesh] OR trends or “case files”).

The other databases were queried using similar terms in key word searches. All searches were restricted to English language publications. We also reviewed reference lists from studies included in the full review to identify additional relevant studies.

To obtain population based disease estimates we downloaded cancer incidence data from 2000 to 2009 from the U.S. NCI (National Cancer Institute) SEER program using the November 2011 release.<sup>17</sup> Case and SEER population data from all 18 registries were used. The University of North Carolina institutional review board exempted this study from review.

### Study Selection and Generation of Misclassification Estimates

Two of us independently reviewed the titles of all articles identified by the search criteria and selected relevant articles for abstract review. We also reviewed all relevant abstracts for study eligibility. There were certain criteria for full text review. 1) The study must report final pathological findings of nephrectomy for renal masses suspected to be RCC. 2) The study must report pathological findings based on mass size on preoperative imaging. In the event of multiple publications on the same patient population we selected estimates from only 1 study to avoid double counting. We selected the most comprehensive study based on level of clinical detail, study duration and number of participating institutions in overlapping multi-institutional series.

If the abstract review did not clearly indicate whether our study inclusion criteria were met, the article was retained for full text review. Review articles describing SRMs were also included to allow identification of additional relevant articles. Two of us independently reviewed the full text of each selected article and applied the previously described inclusion criteria to identify the final set of articles for data extraction.

The total number of benign and malignant tumors for each size category was tabulated to calculate a single pooled percent representing the proportion of BRMs for each size stratum. Main analyses were restricted to only 8 American studies.<sup>16,18-24</sup> Due to differences in size reporting 2 main analyses were performed. Primary analysis was restricted to the most granular size breakdowns (less than 1, 1 to less than 2, 2 to less than 3, 3 to less than 4, 4 to 7 and greater than 7 cm). Secondary analysis included the size strata less than 2, 2 to 4 and greater than 4 cm.

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