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Review Article

Surgical removal of renal tumors with low metastatic potential based on clinical radiographic size: A systematic review of the literature

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Abstract

Introduction: Many patients with small renal masses (SRM) undergo surgical resection of benign and potentially indolent renal masses. We review the available literature to quantify the proportion of renal tumors that are low-risk based on clinical radiographic size, and quantify the number of low-risk masses surgically removed in the United States.

Methods: We systematically reviewed the literature for studies including pathologic findings after excision of renal masses. Inclusion criteria required studies capture both benign and malignant histology at surgical pathology, tumor grade, and stratification by radiographic tumor size. We queried our institutional database using the same parameters. Meta-analysis results were applied to SEER incidence and management data for renal masses. Very-low-risk tumors were defined as benign or grade 1 cT1a, and low-risk tumors as benign, grade 1, or grade 2 cT1a.

Results: A total of 733 titles were reviewed at title screening with 6 full text articles and our institutional database included for meta-analysis. Pooled estimates of benign, very-low-risk, and low-risk tumors were stratified by tumor size: ≤2 cm (25.5%, 40.1%, and 89.3%), 2 to 3 cm (21.2%, 34.1%, and 84.5%), 3 to 4 cm (16.1%, 26.6%, and 77.1%), 4 to 6 cm (11.9%, 23.8%, and 66.4%), and >6 cm (7.2%, 12.6%, and 50.3%). An estimated 3,300 benign, 5,400 very-low-risk, and 13,600 low-risk SRMs were resected in 2014 in the United States.

Conclusion: A substantial portion of patients with SRM are undergoing surgical excision despite harboring tumors of low metastatic potential. The rate of high-grade histology increased with increasing clinical radiographic size, which can be used in counseling and decision-making regarding placement on active surveillance. The number of low-risk SRM removed annually in the United States increased from 8,500 in 2000 to 13,600 in 2014 with stabilization in recent years.

Keywords: Kidney neoplasms; Renal cell carcinoma; Small renal mass; Surgical pathology; Decision making; Active surveillance

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; SRM, Small Renal Mass; cT1a, clinical T1a; RCC, Renal Cell Carcinoma; AS, Active Surveillance

1. Introduction

Approximately 64,000 new cases of kidney cancer were diagnosed in the United States in 2018 [1]. Since the adaptation and widespread use of cross-sectional imaging, the rate of detection of renal masses has increased [2,3]. Moreover, stage migration has occurred so that small renal masses (SRM), clinically localized cortical tumors less than 4 cm (cT1a), account for almost half of all new renal cell carcinoma (RCC) diagnoses [4]. Interestingly, this stage migration has not manifested in an improved cancer-specific mortality for localized RCC, which indicates that many of these incidentally discovered SRM are unlikely to pose significant threat to the patient and suggests the possible overtreatment [2,5,6].

Management and treatment decisions for renal masses are heavily reliant on clinical imaging as renal mass biopsy

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and preoperative tissue sampling has a selective role in the management of clinically localized renal masses suspicious for malignancy [7]. Active surveillance (AS) has emerged as a safe initial management strategy for all patients with tumors less than 2 cm and older patients with comorbidities who have larger tumors [2,7]. Several studies have shown an inverse correlation between radiographic size of renal mass and chance of harboring benign or low-grade pathology in surgical specimens [8−17]. In this study, we performed a systematic review of the available literature to evaluate the association of radiographic renal tumor size with pathologic histology and grade after surgery; in addition, the number of surgically removed renal tumors of low malignant potential in the United States is estimated. This epidemiologic information may have important implications for patient counseling involving management decisions for use of AS and other less invasive treatment modalities for SRM.

2. Methods

2.1. Study selection

MEDLINE, The Cochrane Library, and PubMed were systematically reviewed for all studies (January 2000−December 2017) that included pathologic findings after surgical removal of renal masses. The search was performed using a combination of MeSH Terms and keywords, and the algorithm used is listed in the Appendix. Only reports written in the English language were reviewed. In addition to the output with the above algorithm, references lists were examined for any additional relevant studies.

The titles of all studies identified by the above search method were reviewed for relevance. After title review, pertinent abstracts were reviewed for inclusion. Articles selected for full-text review and inclusion to the meta-analysis were required to have had reported (1) nucleolar grade classification of malignant tumors and (2) number of tumors per grade category with benign tumors stratified by clinical radiographic size. Nucleolar grade was not adjusted if the manuscript was published prior to the establishment of the 2005 ISUP Nucleolar Grade standardization [18]. If multiple publications were included from the same center or the same patient population, the study was selected which had captured more patients over the longest period of time.

To augment the available literate, we queried our institutional database of patients who underwent surgery for a renal mass (2005−2015). Patients who underwent cryoablation or radiofrequency ablation were excluded; biopsy pathology was also excluded. All remaining renal masses were then stratified by clinical radiographic size. Number of benign and low-grade renal masses was determined for each size stratum and percentage of benign and low-grade renal masses out of all renal masses resected in each size stratum was calculated.

2.2. Analysis

The number of benign tumors and tumors representing each pathologic grade as well as total tumors in each size strata were tabulated. The percentage of benign and low-grade tumors was then calculated for each size stratum. Indolent renal masses were defined as “very-low-risk” (clinical T1a: benign or grade 1) and “low-risk” (clinical T1a: benign, grade 1, or grade 2) based on prior literature reporting metastasis-free and cancer-specific survival outcomes exceeding 95% for these renal masses after surgical treatment [8] and a body of literature indicating rates of metastatic disease <1% on surveillance [19]. Very-low-risk tumors capture the proportion of clinical T1a masses that are benign or grade 1 renal cell carcinoma on surgical pathology. Low-risk tumors captures the proportion of clinical T1a masses that are benign, grade 1 renal cell carcinoma, or grade 2 renal cell carcinoma on surgical pathology. Meta-analyses applying random effects modeling and Freeman-Tukey double arcsine transformation were performed for studies meeting all inclusion criteria.

2.3. National burden estimates

Surveillance, Epidemiology, and End Results (SEER; US National Cancer Institute) incidence data for each year from 2000 to 2014 for SEER 18 Registries were used to estimate proportion of patients undergoing management (surgery, thermal ablation, and no intervention) for renal masses. The total incidence of kidney tumors in each year from SEER Cancer Statistics Review was stratified by size and then multiplied by the proportion receiving surgery to estimate the number of masses surgically removed. The proportion of benign or low-grade tumors from the meta-analysis was then applied to the number of surgically removed masses in each size stratum, allowing for an estimation of the number of surgically resected benign or low-grade renal masses in the United States each year.

3. Results

3.1. Study identification

A total of 733 articles were identified for title review and 114 proceeded to abstract review for relevance (Supplemental Figure 1). Abstracts were excluded for the following reasons: if they did not define pathologic grade, if they did not list pathologic grade or benign pathology by stratified size, if the study was limited to only partial nephrectomy pathology specimens, if the article selected only malignant tumors, and/or if the study included pathology from biopsy results. Of the 114 abstracts reviewed, 50 (44%) were excluded because they did not contain pathologic data, 34 (30%) were excluded because they did not stratify pathologic data by clinical radiographic size, 9 (7%) were excluded because they were irrelevant, 4 (3%) were excluded because they were not limited to clinically localized masses, and 1 (1%) was excluded due to no available full text source. Sixteen articles proceeded to full text review with 2 (13%) excluded for including duplicate data already represented in another study, 7 (44%) excluded due to incomplete size-stratification, and 1 (6%) excluded for absence of benign pathology. Six full text articles including tumor histology (benign and malignant), tumor grade, and tumor size stratification were included [8,9,11,12,15,16]. From our institutional database, 2,080 patients undergoing either partial or radical nephrectomy were identified and stratified by clinical radiographic size.

3.2. Pooled estimates and meta-analysis

Data for 7,143 patients was analyzed from included studies providing sufficient tumor size stratification and tumor grade data. Pooled proportions of benign and low-grade tumors were tabulated for all included studies (Fig. 1). One study only reported Fuhrman grading for a subset of patients with clear cell RCC, so sample sizes for benign and low-grade tumors were adjusted based on the total sample size to project the number of low-grade tumors onto the full sample of malignant tumors [8].

Meta-analysis results are detailed in Supplemental Figures 2 and 3. The proportion of benign tumors decreased with increasing tumor size: 25.5% (≤2 cm), 21.2% (2−3 cm), 16.1% (3−4 cm), 11.9% (4−6 cm), and 7.2% (>6 cm). When considering both benign and low-grade (grade 1) tumors, the proportions were 40.1% (≤2 cm), 34.1% (2 to 3 cm), 26.6% (3−4 cm), 23.8% (4−6cm), and 12.6% (>6 cm). Relaxing the criteria to allow grade 2 tumors (benign + grade 1 + grade 2), the proportions increased to 89.3% (≤2 cm), 84.5% (2 to 3 cm), 77.1% (3−4 cm), 66.4% (4−6 cm), and 50.3% (>6 cm). Fig. 2 display the ratio of masses with indolent pathology to potentially lethal tumors by size strata.

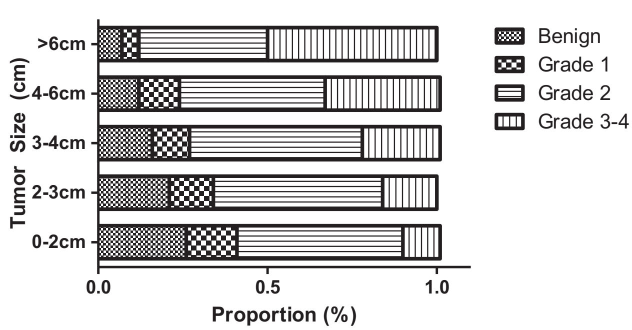

Fig. 1. Graphical depiction of the proportion of benign and nucleolar grade 1 through 4 renal masses stratified by size.

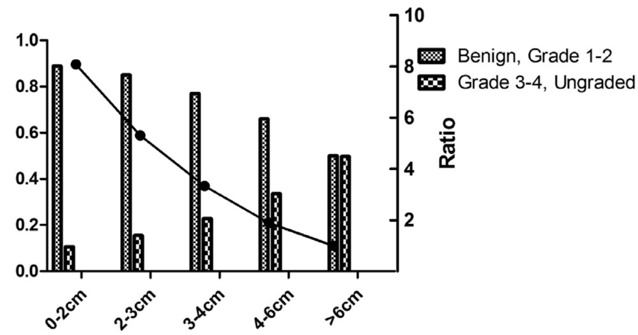

Fig. 2. Ratio of indolent to potentially lethal tumors stratified by size.

3.3. National burden estimates

The number of patients with cT1a benign, very-low-risk, and low-risk renal masses who underwent intervention increased over time (Table 1). Of all patients with cT1a disease, the number of benign tumors resected rose from 2,080 to 3,393, very-low-risk tumors from 3,352 to 5,452, and low-risk from 8,512 to 13,631 between 2000 and 2014 based on distribution data from all included studies. When excluding one European study (Remzi et al.[6]) estimates for the United States from 2000 to 2014 remain similar with increase of 2,041 to 3,337 benign tumors, 3,317 to 5,402 very-low-risk tumors, and 8,505 to 13,624 low-risk tumors. Notably, the overall incidence of kidney cancer has plateaued in recent years; while the United States population increased steadily over time, the proportion of masses surgically resected decreased across size strata in comparison to AS and thermal ablation (Fig. 3). Therefore, a stable number low-risk and very-low-risk masses were resected from 2008 onward (Fig. 3).

4. Discussion

The growing number of incidentally detected SRM poses an important management dilemma. The smaller the size of the renal lesion on radiographic imaging, the higher the probability of diagnosing it as a benign or indolent neoplasm after surgical resection and pathologic evaluation [8−17]. In addition, nucleolar grade is a significant independent prognostic factor for RCC [19,20]. Studies have shown a significant association between grade and cancer-specific survival with 5-year cancer-specific survival >90% for grade 1 and grade 2 tumors and a sharp drop-off to <55% with grade ≥3 tumors [21]. We demonstrate that among tumors measuring <3 cm, only 10% of renal masses harbor high grade (grade 3 or grade 4) pathology and 40% of renal masses are benign or grade 1. As hypothesized, the likelihood of having high-grade disease increases as the size of the renal mass increases. Nevertheless, many SRM are removed routinely without preoperative pathologic diagnosis, leading to significant overtreatment, and potentially unnecessary morbidity and cost. We demonstrate the

Table 1
Estimated number of surgically resected benign, very low risk (benign + grade 1), and low risk (benign + grade 1 + grade 2) clinically localized renal masses stratified by size applying meta-analysis results to the Surveillance, Epidemiology, and End Results Program (2000−2014)

Year	Benign						Very low risk						Low risk					
	≤2 cm	2−3 cm	3−4 cm	4−6 cm	>6 cm	Total	≤2 cm	2−3 cm	3−4 cm	4−6 cm	>6 cm	Total	≤2 cm	2−3 cm	3−4 cm	4−6 cm	>6 cm	Total
2000	610	827	643	751	749	**3,580**	959	1,330	1,063	1,502	1,310	**6,165**	2,135	3,296	3,081	4,192	5,231	**17,935**
2001	632	853	712	761	746	**3,704**	994	1,372	1,177	1,521	1,305	**6,370**	2,214	3,400	3,411	4,245	5,210	**18,481**
2002	730	932	739	767	735	**3,903**	1,148	1,500	1,221	1,533	1,286	**6,687**	2,556	3,716	3,539	4,278	5,132	**19,221**
2003	810	1,060	716	800	790	**4,176**	1,273	1,705	1,182	1,601	1,383	**7,144**	2,835	4,224	3,427	4,466	5,522	**20,475**
2004	869	1,015	778	811	750	**4,224**	1,366	1,633	1,286	1,622	1,313	**7,220**	3,042	4,047	3,728	4,525	5,241	**20,583**
2005	897	1,102	787	847	758	**4,391**	1,411	1,773	1,300	1,693	1,327	**7,504**	3,142	4,393	3,769	4,725	5,296	**21,325**
2006	1,063	1,193	801	887	767	**4,711**	1,672	1,918	1,323	1,774	1,343	**8,030**	3,723	4,753	3,835	4,950	5,360	**22,621**
2007	1,168	1,255	907	925	796	**5,051**	1,837	2,019	1,498	1,849	1,393	**8,597**	4,091	5,003	4,342	5,159	5,562	**24,157**
2008	1,207	1,308	927	956	793	**5,190**	1,898	2,104	1,531	1,912	1,387	**8,831**	4,226	5,213	4,438	5,334	5,537	**24,748**
2009	1,228	1,291	830	905	768	**5,021**	1,930	2,077	1,371	1,811	1,344	**8,532**	4,299	5,146	3,972	5,051	5,366	**23,834**
2010	1,094	1,237	824	918	742	**4,815**	1,720	1,990	1,361	1,836	1,299	**8,207**	3,831	4,931	3,945	5,123	5,185	**23,016**
2011	1,179	1,312	920	918	775	**5,105**	1,855	2,110	1,520	1,836	1,356	**8,677**	4,130	5,229	4,406	5,123	5,413	**24,302**
2012	1,284	1,352	844	975	781	**5,235**	2,019	2,174	1,394	1,949	1,367	**8,904**	4,496	5,387	4,040	5,439	5,459	**24,821**
2013	1,224	1,330	896	960	741	**5,150**	1,924	2,139	1,480	1,919	1,297	**8,760**	4,285	5,301	4,289	5,355	5,179	**24,409**
2014	1,215	1,313	866	926	762	**5,081**	1,910	2,111	1,430	1,852	1,334	**8,637**	4,254	5,232	4,145	5,166	5,324	**24,121**

number of surgically resected benign, very-low-risk, and low-risk tumors increased from 2000 to 2008; notably, the number stabilized from 2008 to 2014 which may be due to re-evaluation of the treatment paradigm in recent years for SRM with low metastatic potential.

Radiographic size is the most accessible and frequently used parameter for pretreatment decision-making among patients presenting with renal masses. Radiographic and pathologic size are closely correlated, making preoperative imaging a reasonable tool for predicting probability of adverse pathology [22]. Nomograms have been developed looking at other factors potentially associated with aggressive disease including age, symptomatic presentation, male sex, and family history, but tumor size and patient sex remain the only consistent predictors of malignant pathology based on a recent review of the literature [23]. While we have quantified the proportion of potentially indolent tumors by size, the risk of clinical upstaging should also be considered in patient counseling. Studies included in the present review did not consistently quantify the risk for upstaging to ≥pT3a, but a prior analysis provides estimates of 4.5% for cT1a, 9.5% for cT1b, and 19.5% for cT2 tumors [24]. Additional institutional studies in the literature support these estimates with one noting 5% of cT1b patients are upstaged to pT2 and 9.8% to ≥pT3a [25,26]. The increasing risk of upstaging with tumor size may further support a decision to pursue surgery for tumors >4 cm in size and especially for tumors >7 cm in size.

AS has been proposed as a reasonable initial management option for patients with SRM and is most often used in the elderly and comorbid population given they carry more risks to balance during treatment selection [7]. AS protocols were initially developed based on studies looking at linear growth rate, although reported growth rates among AS series have been variable and unreliable in indicating high-grade tumors or those with higher malignant potential [27]. Up to 30% of masses followed under AS have been shown to undergo no radiographic growth, and of these, none progressed to metastasis [19,28]. As the body of literature surrounding AS in RCC matures, clinical and radiologic criteria will likely be defined to predict tumor behavior and differentiate indolent from more aggressive tumor biology. The argument can be made that patients with SRM less than 2 to 3 cm can be counseled and considered for a less invasive management strategy like AS due to lower risk of high-grade pathology. The indications and demographics of patients selected for AS may be expanded in the future to include younger and healthier patients with SRM given the evolving data demonstrating safety of surveillance coupled with the probability that these patients harbor indolent or benign tumors [20].

There are several limitations to the present study. Selection bias exists, as all included studies are retrospective and limited to patients with clinically localized disease undergoing surgical extirpation at tertiary care and academic centers. Patients with clinical evidence of metastatic or

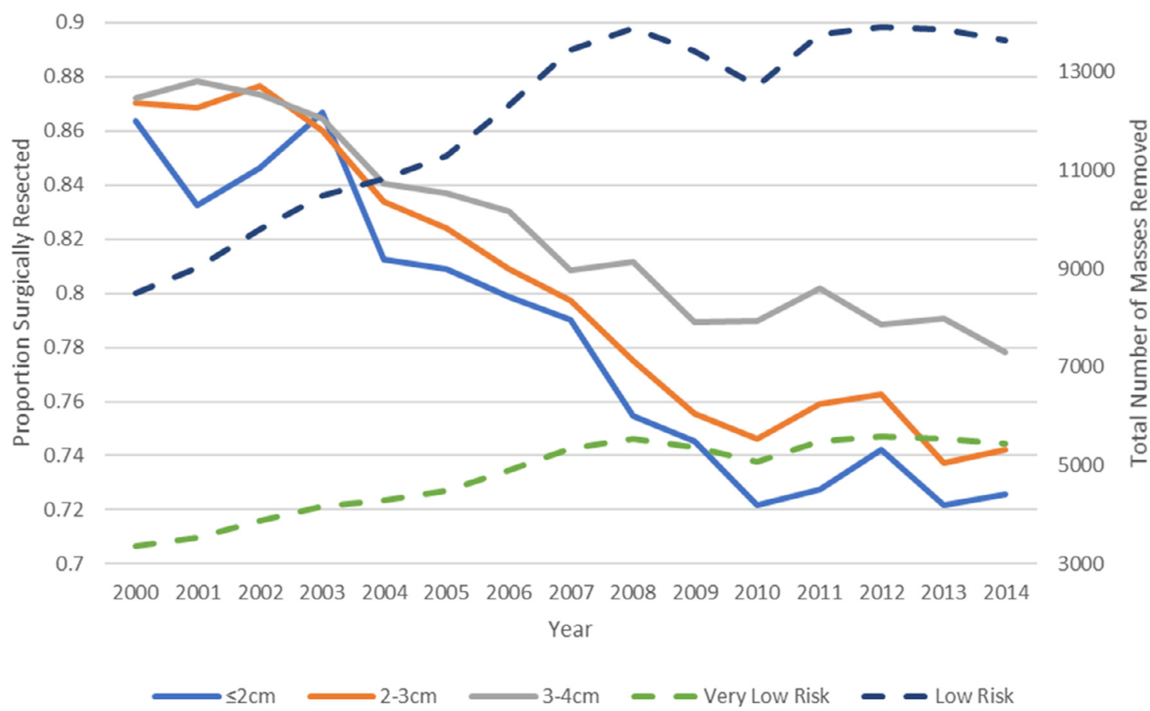

Fig. 3. The proportion of cT1a renal masses surgically resected per year stratified by size (solid lines − left-sided vertical axis) and total number of mass surgically removed by risk category (dashed lines − right-sided vertical axis) from 2000 to 2014 (Surveillance, Epidemiology, and End Results Program).

regional lymph node disease were excluded as they most likely to harbor aggressive pathology and deserve prompt treatment. Histologic grading was obtained from studies across different years which may vary in consistency and reliability of tumor grade reporting. Definitions for nucleolar grade have change over time with the most recent ISUP classification no longer grading chromophobe RCC and sarcomatoid tumors automatically labeled grade 4 [29]. While studies included in the meta-analysis span different iterations of grading schema, the definition of low-grade tumors has remained stable. In addition, histologic subtype information was inconsistently reported across studies and could not be analyzed as reliably as grade. However, as chromophobe (not graded) and papillary RCC typically impart a survival advantage over clear cell RCC, our meta-analysis may underestimate the number of indolent cancers per size stratum [19]. Lastly, other patient factors including presentation, age, and sex, which impact management decisions, were not consistently reported in studies to include in analysis. Future reports on surgically resected renal masses should include clinical and pathologic stage, histologic subtype, and grade as well as long-term clinical oncologic outcomes [30].

5. Conclusions

A substantial portion of patients with SRM are undergoing surgical excision despite harboring tumors of benign histology or low metastatic potential. The proportion of patients found to have high-grade RCC increases with increasing renal mass size on preoperative cross-sectional imaging. Clinical radiographic size can estimate a patient's risk of benign or indolent pathology and be used in counseling and decision-making regarding placement on AS in addition to age and comorbidity. The number of low-risk SRM removed annually in the United States increased from about 8,500 in 2000 to 13,600 in 2014 and has stabilized in recent years.

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.05.013.

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