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Urologic Oncology: Seminars and Original Investigations ▮ (2016) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

The metastatic potential of renal tumors: Influence of histologic subtypes on definition of small renal masses, risk stratification, and future active surveillance protocols

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Received 8 August 2016; received in revised form 6 November 2016; accepted 13 November 2016

Abstract

Objective: The influence of histology in metastatic potential is often overlooked when discussing the management options of small renal masses (SRM), with size or growth rate often serving as the triggers for the intervention. We aim to re-examine the definition of a SRM by evaluating the metastatic potential of renal masses incorporating tumor size and histology to create metastatic risk tables.

Materials and methods: Surveillance Epidemiology and End Results (SEER)-18 registries database was queried for all cases of clear cell, papillary, and chromophobe renal cell carcinoma (RCC) diagnosed between 2004 and 2012. There were 55,478 cases identified that included 43,783, 8,587, and 3,208 cases of clear cell, papillary, and chromophobe, respectively. Tumors were stratified using 1-cm increments to determine the metastatic potential by calculating the metastatic rate at presentation for different size intervals in histologic categories.

Results: For all 3 histologies, tumors measuring 5 cm or less had a rate of metastatic RCC at presentation of less than 4%. The metastatic potential was highest for clear cell, followed by papillary and then chromophobe tumors. Setting a cutoff of no more than 3% for metastatic potential to be called a SRM, makes clear cell carcinoma and papillary carcinoma a SRM up to 4 cm, whereas the chromophobe RCC would be considered a SRM up to 7 cm.

Conclusion: Although clinical staging and tumor size have been the key determinants in decision-making of patients with solid renal tumors, the histology-specific risks of metastatic potential are different for each mass. The definition of a SRM should be based on the metastatic potential and not on tumor size alone. This information could be helpful for counseling and managing patients with SRMs as well as for modifying active surveillance protocols. © 2016 Elsevier Inc. All rights reserved.

Keywords: Renal cancer; Renal biopsy; Histology; Synchronous metastasis; Tumor size

1. Introduction

The increased utilization of cross-sectional imaging has increased the incidence of renal cell carcinoma (RCC) throughout the past 30 years. It has been estimated for 2016 that approximately 62,700 new patients would be diagnosed with RCC, more than 60% incidentally, and approximately 14,240 patients would die of RCC [1]. Despite the fact that significant numbers of patients present with advanced or metastatic RCC (mRCC), most are diagnosed with localized renal tumors, with smaller tumors often referred to as small renal masses (SRMs). Although the traditional AJCC staging system uses tumor size to stratify the risk of Cancer-Specific Survival (CSS), prior studies have shown differences in CSS based on histology after surgical treatment [2–4].

With increased utilization of active surveillance (AS) and increased awareness of competing mortality risks, the definition of SRM may need to be reconsidered. Should a SRM be based on size alone, such as 3 or 4 or 5 cm? Or is a SRM a tumor that carries a certain metastatic potential? Contemporary management strategy is still largely based on

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http://dx.doi.org/10.1016/j.urolonc.2016.11.009
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patient preference, comorbidities, tumor size, location, and growth kinetics. The influence of histology in metastatic potential is often overlooked when discussing management options, with size or growth rate often serving as the only triggers for intervention.

In this study, we evaluate the metastatic potential for renal masses based on histology, and hypothesize that the histology of small masses influences the rate of metastatic spread, thus refining the definition of the SRM based on potential for development of metastatic disease progression rather than the size alone.

2. Materials and methods

Surveillance Epidemiology and End Results (SEER)-18 registries database was queried for all patients ≥20 years of age diagnosed with RCC between 2004 and 2012. Several non–clear cell RCC subtypes were added to the International Classification of Diseases for Oncology (ICD-O) code set in 2000 and used starting in 2001 and an updated coding schema was implemented starting in 2004. There were 115,347 renal tumors during this time frame. To minimize rare and mixed histologies, we included only clear cell (8,310), papillary (8,260), and chromophobe (8,317) histologies in analysis, yielding 67,388 tumors. Renal Cell Carcinoma, NOS (8,312) that does not distinguish between histologic subtypes constituted 29,786 renal tumors and was excluded from analysis. There were only 18,173 tumors that were not grouped into any of the aforementioned histologies, of which 7,631 (6.6% of the entire cohort) were urothelial in origin. Final analyses were performed on tumors up to 20 cm, known tumor size, grade, and complete TNM staging.

Patient demographic variables included age, sex, and race. Tumor variables included grade, histology, stage, and size. Patients were then divided into cohorts according to tumor histology. Within the histology-specific cohorts, patients were further subdivided to those who had localized disease (N0M0) and those with metastatic disease (N+ or M+ or both N+ and M+). Tumors were stratified by size into groups of 1-cm increments to create metastatic renal mass tables. Additionally, a scatter plot was created that compared tumor size and metastatic rate at presentation for each histology, including Renal Cell Carcinoma, NOS. Tumors smaller than 1 cm were not included in the metastatic renal mass tables and the scatter plot, as these masses would be considered indeterminate. From prior large series and meta-analysis on AS, the metastatic events occurred in up to 2.0% [5,6]; therefore, we used a cutoff of up to 3% for an acceptable metastatic rate as this series is likely enriched for potential metastatic events and these patients were not on true AS. Statistical significance was set at $P \leq 0.05$. Stata 14 statistical software was used to perform statistical analysis. Univariate and multivariable analyses were performed to identify patient factors and tumor characteristics associated with metastatic disease.

3. Results

A total of 55,478 cases met our inclusion criteria and included 43,683, 8,587, and 3,208 cases of clear cell, papillary, and chromophobe RCC, respectively. A total of 54,191 (97.7%) were surgically treated. The mean patient age was 61.2 years (range: 20–108) and 63.7% of patients were male. Mean and median tumor size was 5.2 and 4.2 cm, respectively. Table 1 describes patient demographics and tumor characteristics.

Among those with known histology, there were 4,369 (7.9%) who presented with metastatic disease. When looking at only tumors <7 cm, the metastatic rate was 3.1%, and for all tumors <10 cm, the metastatic rate was 5.3%. The metastatic rate varied according to histology with 8.7%, 5.5%, and 2.9% of patients presenting with metastatic disease for clear cell, papillary, and chromophobe RCC, respectively ($P < 0.0001$). The median size of tumors in patients with mRCC (8.8 cm) was significantly higher than those with localized RCC (4.0 cm) ($P < 0.0001$). The size of metastatic tumors was different between histologies ($P = 0.015$). Table 2 displays patient demographics and tumor characteristics according to histology, whereas Table 3 displays the univariate and multivariable analyses for tumor and patient characteristics and metastatic disease. Histology remained a significant predictor for association with metastatic disease at presentation.

The rate of metastatic disease at presentation increased as tumor size increased (Table 4). Tumor histology along with

Table 1
Patient demographics and tumor characteristics of all patients and then divided by synchronous metastasis at presentation. The *P* value compares patients with N0M0 stage tumor to patients with metastatic tumor

	All tumors ($n = 55,478$)	N0M0 ($n = 51,109$)	Metastatic ($n = 4,359$)
Age, y			
Mean	61.2	61.2	61.4
Median	62	62	61
Race			
White (%)	45,977 (82.9)	42,274 (83.2)	3,703 (85.0)
Black (%)	5,837 (10.5)	5,478 (10.8)	359 (8.2)
Other (%)	3,664 (6.6)	3,357 (6.6)	297 (6.8)
Sex			
Male (%)	35,365 (63.7)	32,295 (63.2)	3,070 (70.3)
Female (%)	20,113 (36.3)	18,814 (36.8)	1,299 (29.7)
Grade			
Grade 1 (%)	7,373 (13.3)	7,201 (14.1)	172 (3.9)
Grade 2 (%)	29,771 (53.7)	28,637 (56.0)	1,134 (26.0)
Grade 3 (%)	15,287 (27.6)	13,274 (26.0)	2,013 (46.1)
Grade 4 (%)	3,047 (5.5)	1,997 (3.9)	1,050 (24.0)
Histology			
Clear cell (%)	43,683 (78.7)	39,882 (78.0)	3,801 (87.0)
Papillary (%)	8,587 (15.5)	8,113 (15.9)	474 (10.8)
Chromophobe (%)	3,208 (5.8)	3,114 (6.1)	94 (2.1)
Tumor size, cm			
Mean	5.2	4.8	9.0
Median	4.2	4.0	8.8

This table does not include the *P*-Values for the comparison. $P = 0.28$ for age. $P < 0.0001$ for all other comparisons.

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